"ASSOCIATION OF SERUM LIPID LEVELS WITH DIABETIC RETINOPATHY IN A TERTIARY CARE CENTRE IN TAMIL NADU"

Dissertation submitted by

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In partial fulfillment of the requirements for the degree of

MASTER OF SURGERY

IN

OPHTHALMOLOGY

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DEPARTMENT OF OPHTHALMOLOGY

PSG INSTITUTE OF MEDICAL SCIENCES & RESEARCH

COIMBATORE

DECLARATION BY THE CANDIDATE

I hereby declare that this dissertation entitled "**ASSOCIATION OF SERUM LIPID LEVELS WITH DIABETIC RETINOPATHY IN A TERTIARY CARE CENTRE IN TAMIL NADU"** is a bonafide and genuine Research work carried out by me under the guidance of **DR. D. SUNDAR, M.S.,D.O.** Professor and Head of the Department of Ophthalmology, PSG institute of Medical Sciences & Research. Coimbatore in partial for the award of M.S. Degree in Ophthalmology to be held in 2014. This dissertation has not been submitted in part of full to any other University or towards any other degree before this below mentioned date.

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ASSOCIATION OF SERUM LIPID LEVELS WITH DIABETIC RETINOPATHY IN A TERTIARY CARE CENTRE IN TAMIL NADU

ABSTRACT

AIM OF THE STUDY

Primary Aim: To study association between serum lipid levels & severity of Diabetic retinopathy

Secondary Aims:

To assess the proportion of patients with dyslipidemia among patients with diabetic retinopathy

To assess association between various types of lipoproteins with diabetic retinopathy

MATERIALS AND METHODS

This is a prospective observational study conducted among patients attending Ophthalmology OPD in a tertiary care hospital.It is a cross-sectional,hospital based study spanning over a period of 18 months from June 2011 to November 2012.100 type 2 diabetic patients attending Ophthalmology OPD were examined by ophthalmoscopy and fundus fluorescein angiography.Their diabetic retinopathy status was graded according to ETDRS classification.Their serum lipid levels were

assessed.Association between serum lipid levels and retinopathy severity were assessed using SPSS software.

RESULTS:

In our study the incidence of diabetic retinopathy was 55% and 45% had no features of diabetic retinopathy. In our study, 45% had no signs of diabetic retinopathy, 46% had non-proliferative retinopathy and 9% had proliferative retinopathy. Mean age in the no diabetic retinopathy group was 54.02,in NPDR group it was 57.56 and in the PDR group it was 55.55. According to our study,the mean total cholesterol levels are 177.22 in diabetics without retinopathy, 186.86 in NPDR and 159.33 in PDR. 20 of the 55 patients (36.3%) with retinopathy had elevated serum total cholesterol levels.63.6% of retinopathy patients had desirable cholesterol levels.The mean triglyceride levels were calculated as 141.97 in diabetics without diabetic retinopathy, 163.13 in NPDR and 195.00 in PDR patients. The mean HDL values were 39.73 in diabetics without diabetic retinopathy, 36.80 in NPDR and 31.66 in PDR. Mean LDL levels in diabetics without diabetic retinopathy was 113.13, 116.04 in NPDR and 99.33 in PDR. 22 of 55 retinopathy cases (40%) had optimal levels of LDL.Mean glycosylated haemoglobin level was 8.12 in diabetics without retinopathy, 8.74 in NPDR AND 10.00 in PDR . Mean Fasting blood glucose level was 154.22 in diabetics without retinopathy, 169.63 in NPDR and 191.11 in PDR. Mean creatinine level was 0.75

in diabetics without retinopathy, 0.80 in NPDR and 0.86 in PDR. Mean serum haemoglobin is 13.33 in diabetics without retinopathy, 13.17 in NPDR and 11.87 in PDR.

CONCLUSION:

No significance was found with severity of diabetic retinopathy and total serum cholesterol, serum triglyceride,HDL and LDL levels.Of the retinopathy patients, 36.3% had elevated serum total cholesterol levels, 70.9% had low HDL and 60% elevated LDL levels.No significant association was found between severity of diabetic retinopathy and fasting blood glucose levels and also serum creatinine levels.There was significant association between glycosylated hemoglobin and diabetic retinopathy severity.And also significant negative association with haemoglobin levels and severity of diabetic retinopathy

KEY WORDS: Diabetic retinopathy, cholesterol, HDL, LDL, triglycerides

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PART –I

INTRODUCTION

INTRODUCTION

In the year 2000,the number of people with diabetes in the world was 171 million.By the year 2030,the numbers are predicted to reach 366 million.In India,the prevalence of type2 DM is different in different regions and is estimated to be 5-14%. In 2000,31 million were diabetic in India and predicted to hike to 79 million by 2030.Thus India is apparently the diabetes capital of the world and is likely to remain so for 30 years.

Diabetics are likely to suffer from various macrovascular and microvascular complications of which diabetic retinopathy is a well established microvascular complication. Prevalence of Diabetic retinopathy was found to be 50.3% in USA, 33.6% in UK, 29.0% in Australia and 17.6% in India.

The large numbers of people affected with DR is an indication of the severity of the problem. Various factors have been implicated in the development and progression of diabetic retinopathy.

The association between serum lipid levels and DR have been widely studied but has produced conflicting results which may have been because of differences in the methodology adapted and also maybe the ethnicity. Our study mainly focuses on the South Indian population and thus reducing the errors due to changes in ethnicity.

Since the visual disability from diabetes is preventable and treatable, awareness of the problem and early detection and management can preserve the quality of life. If there is a significant role of lipid levels in diabetic retinopathy, control of the former could be beneficial for the latter.Our study aims to bring out a clearer picture of this scenario in South India.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. [1]

Epidemiology

In the year 2000,the number of people with diabetes in the world was 171 million.By the year 2030,the numbers are predicted to reach 366 million.In India,the prevalence of type2 DM is different to different regions and is estimated to be 5-14%.In 2000,31 million were diabetic in India and predicted to hike to 79 million by 2030.Thus India is apparently the diabetes capital of the world and is likely to remain so for 30 years.

The reason for the increase in number of cases is predicted to be a result of an aging global population, urbanization ,a rising prevalence of obesity, and sedentary lifestyles[3].

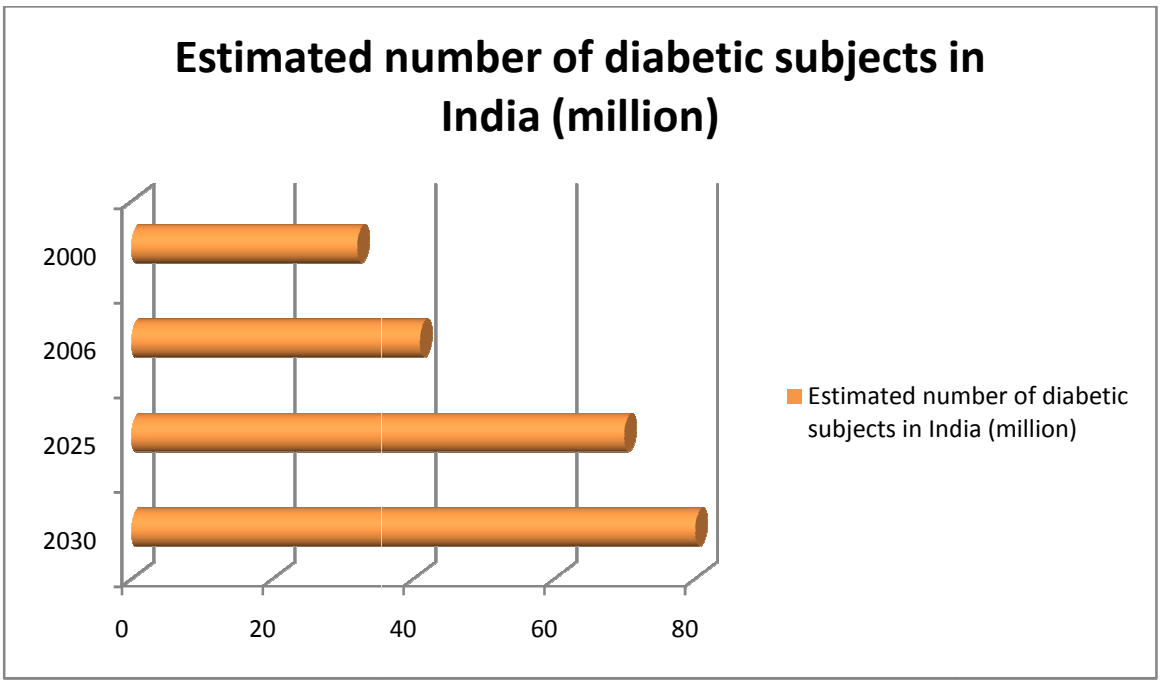


Fig. 1. Estimated number of diabetic patients in India in millions [2,3]

Types:[1]

1.*Type 1* (Insulin dependant diabetes mellitus [IDDM], Juvenile onset diabetes) – This develops more commonly between 10 and 20 years of age and presents with acute polydipsia, polyuria, nocturia and weight loss. Association with HLA-DR3 and HLA-DR4 is seen.Pathogenesis is the autoimmune destruction of pancreatic islet cells which produce insulin.Type 1 diabetics often manifest a total lack of insulin and hence are dependent on external insulin for sugar metabolism.

2.*Type 2* (Non-Insulin dependent diabetes mellitus [NIDDM],Maturity onset diabetes) – This manifests most frequently by 50-70 years.They have relative

deficiency of Insulin and/or peripheral insulin resistance.They are often asymptomatic and discovered by chance.

Diagnostic tests for Diabetes[1]:

- Fasting blood sugar > 126mg%
- Random blood sugar >200mg%
- Glucose tolerance test is performed if diagnosis is uncertain
- Glycosylated haemoglobin (HbA1C) reflects the average level of blood glucose over the last 6 weeks.Normal value is 4-8%.Values more than this indicates inadequate glycemic control.
- Urine testing for glycosuria is an unsatisfactory method of monitoring diabetic control.

Ophthalmic manifestations of Diabetes:[4]

1.Ocular conditions directly associated with Diabetes

- Cataract
- Anterior Ischemic Optic Neuropathy
- Diabetic papillopathy
- Extraocular movements disorders

2.Ocular conditions for which diabetes is a known risk factor

- Glaucoma – Primary open angle and Neovascular
- Ocular Ischemic syndrome

3.Ocular conditions for which diabetes is a possible risk factor

- Retinal vein occlusion
- Retinal arteriolar emboli
- Retinal artery occlusion
- Corneal disease

4.Conditions masquerading as diabetic retinopathy in diabetics

- Age related macular degeneration
- Hypertensive retinopathy
- Radiation retinopathy

DIABETIC RETINOPATHY RISK FACTORS

Diabetic retinopathy (DR) is more common in type 1 DM (40%) when compared to type 2 (20%).

1. ***Duration of Diabetes***: Incidence of DR in patients diagnosed with diabetes before the age of 30 years,is 50% after 10 years and 90% after 30 years.It rarely

develops within 5 years of onset of DM or before puberty though about 5% of type 2 DM have DR at presentation.[5]

2. ***Control of Blood Glucose*:** Good glycemic control protects against development of retinopathy.Glycosylated Hemoglobin at baseline is a strong and independent risk factor or Diabetic Macular edema. DCCT recommends intensive therapy to achieve near normal glycemic status as early as possible in IDDM patients[6]. The phenomenon of ongoing beneficial effects on diabetic complications after a period of improved glycemic control even if followed by a return to usual (often poorer) metabolic control has been described as representing "metabolic memory" by the DCCT/EDIC investigators[7] and as a "legacy effect" by the UKPDS investigators[8].Early insulinisation has been recommended by Ranjit Unnikrishnan I, Anjana RM, Mohan V based on the above concepts[9].

3. ***Hypertension:*** Patients with DM commonly suffer from concomitant hypertension.The Wisconsin Epidemiology Study of Diabetic Retinopathy (WESDR) found that patients with type 1 DM had a 17% prevalence of hypertension at baseline and a 25% incidence after 10 years[10].Among type 2 DM patients,cross-sectional studies revealed a hypertension prevalence of 38% to 68%.

Patients with hypertension are more likely to develop DR and even more severe levels and have more rapid progression.They are also reported to be upto 3 times more likely to develop diffuse DME.Both systolic and diastolic pressures seem to have an association with DR. A causal relationship between DR and hypertension was strongly suggested by the United Kingdom Prospective Diabetes Study (UKPDS)[11].The UKPDS was a large randomized prospective clinical trial evaluating the effects of rigorous BP control in addition to glycemic control on the prevention and progression of diabetic vasculopathy in patients with type 2 DM.Tight BP control is said to have beneficial effect by decreasing the risk of clinical complications from diabetic eye disease.[12] The UKPDS showed that the incidence of retinopathy was associated with systolic blood pressure[11,12], while in the WESDR, diastolic blood pressure was a significant predictor of progression of diabetic retinopathy to PDR over 14 yr of follow up in patients type 1 diabetes[10]. In the Indian context, hypertension was not a significant confounding factor in the CURES Eye study[13].

4.***Renal Disease****:* There are extensive cross-sectional and longitudinal studies reporting a relationship between proteinuria or microalbuminuria and retinopathy.

In the Microalbuminaria Collaborative Study Group report, retinopathy was not a significant independent predictor of albuminaria when adjusted for other baseline predictive variables including HbA1c, mean arterial pressure, gender

and smoking status[14].Some of the effects of renal disease on DR may be confounded by blood pressure (due to close correlation between kidney disease and hypertension) or DM duration due to the high prevalence of DR and other coexisting complications with increasing duration of DM.

Nevertheless the presence and severity of DR are indicators of the risk of gross proteinuria as evidenced by the WESDR which revealed that half of all type 1 DM patients with PDR and 10 or more years of DM had concomitant proteinuria.[10] The presence of gross proteinuria at baseline is associated with 95% increased risk of developing DME among type 1 patients in the WESDR.

Gross proteinuria is a risk indicator for PDR in younger onset DM patients and therefore regular eye checkups are advised in that group[15]. Individuals with macroalbuminuria in comparison to microalbuminuria and normoalbuminuria showed greater DR prevalence and severity[16].

5.*Serum lipids* : Dyslipidemia,though a clear risk factor in diabetic renal disease,its effect on DR and macular edema are less certain. The studies conducted on this subject show diverse outcomes.

ETDRS report 22 states that those diabetics with increased total cholesterol, LDL or Triglyceride levels are more likely to have or develop retinal hard exudates, which can be associated with risk of vision loss, independent of the extent of macular edema.They also stated that the risk was two fold in cases

with elevated serum LDL-c and total cholesterol levels.[17]Klein et al inferred that this relationship was not applicable to type 2 diabetics that did not use insulin, and was seen in type 1 diabetics only.[18]

According to the DCCT/EDIC cohort the severity of retinopathy was positively associated with triglycerides and negatively associated with HDL cholesterol in type 1 diabetics.[19]The CURES Eye Study showed association of diabetic retinopathy with total cholesterol and serum triglycerides and also that diabetic macular edema showed a string correlation with high LDL levels.[20]

A randomized controlled trial on the role of atorvastatin in diabetic maculopathy concluded that there was a decrease in the visible retinal lipid exudates and also a positive effect on the visual outcome of affected patients.[21]

FIELD study showed a 30% reduction in laser interventions required in type 2 diabetic patients receiving fenofibrate, which reduces lipid levels, versus the placebo group. [22] These studies therefore show that control of lipid levels could help in control of diabetic retinopathy.

6.*Pregnancy* *:* Though DR can progress rapidly during pregnancy, this is usually a transient progression and long term risk of progression of DR is not increased. Both the Diabetes in Early Pregnancy study[23],a prospective study of 140 pregnant diabetic patients, and the DCCT[24], a prospective study that

included 680 female diabetic patients of child bearing age, found that women with poorest glycemic control at baseline and greatest reduction in HbA1C in the first trimester were at increased risk of retinopathy progression. Also the increasing severity of DR at baseline adversely affects pregnancy outcome, including high incidence of pregnancy induced hypertension, obstetrical complications, fetal malformations and/or fetal death. A study conducted on type 1 diabetics concluded that progression of DR in pregnancy is uncommon (5%) but there is a significant increase if duration of DM is more than 10 years and also moderate- severe DR at baseline.[25]

7.*Anemia*: There have been case reports which show an association between anemia and DR. Low hematocrit was an independent risk factor in the ETDRS analysis of baseline risk factors for development of high-risk PDR and of severe visual loss. In patients with retinopathy, those with low hemoglobin levels had a fivefold increased risk of severe retinopathy as compared with those with higher hemoglobin levels.[26,27,28]

8.*Genetic factors:* Strong associations have been found between proliferative retinopathy and presence of HLA-DR phenotypes 4/0, 3/0 and x/x[29]. ICAM-1 469KK genotype was associated with a 3.51-fold increased risk for retinopathy.[30]

Aldose Reductase Gene (ALR2), Vascular Endothelial Growth Factor Gene (VEGF),Receptor for Advanced Glycation End Products Gene (RAGE) are some other genes implicated in the development of diabetic retinopathy.[31]

Retinopathy Factors reducing the prevalence and severity of Diabetic Retinopathy : Causes of asymmetric DR :[5,32,33]

1. Glaucoma : Reduces the prevalence and severity of DR in affected eyes.Underlying mechanism is unclear though there are several suggested possibilities:

- Loss of metabolic activity in retina with degeneration of ganglion cells secondary to chronic glaucoma.
- Loss of retinal vascular perfusion secondary to elevated intraocular pressure.

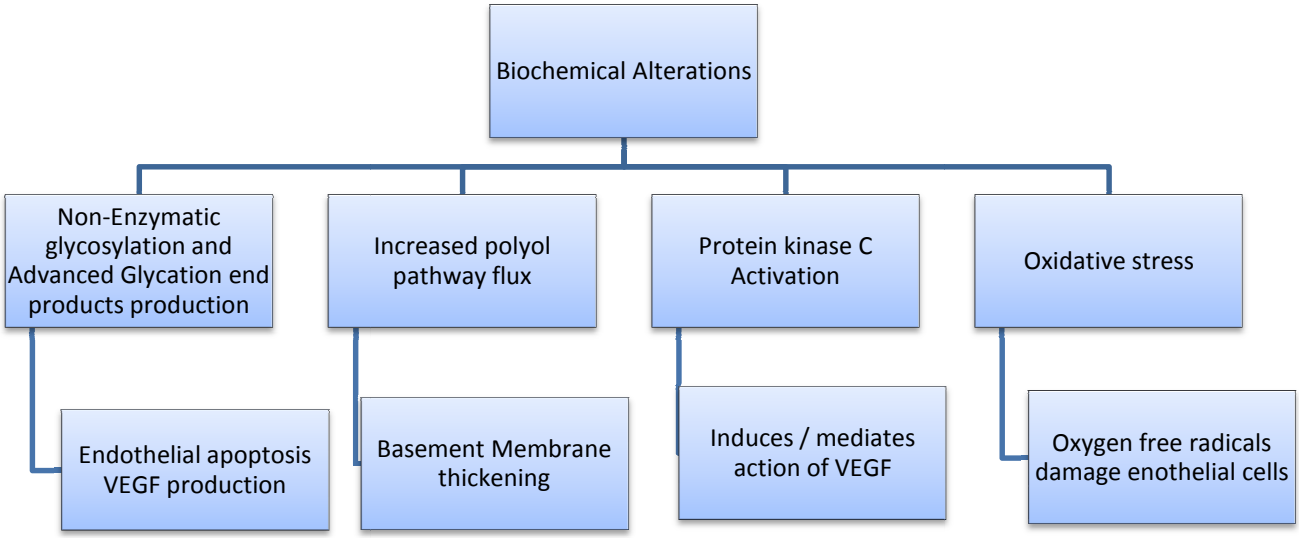
2. Myopia : Myopia of atleast 5 Dioptres is known to reduce the severity and prevalence of DR.
3. Carotid arery stenosis : Cases of unilateral narrowing of internal carotid artery resulting from atherosclerosis has been found to be protecting the ipsilateral eye from developing diabetic retinopathy.
4. Retinochoroidal scarring : Eyes with retinochoroidal scarring from trauma, inflammatory diseases etc has markedly reduced prevalence and severity of DR. The resultant decreased retinal metabolism and a decreased need for oxygen would result in diminished production of angiogenic factors.

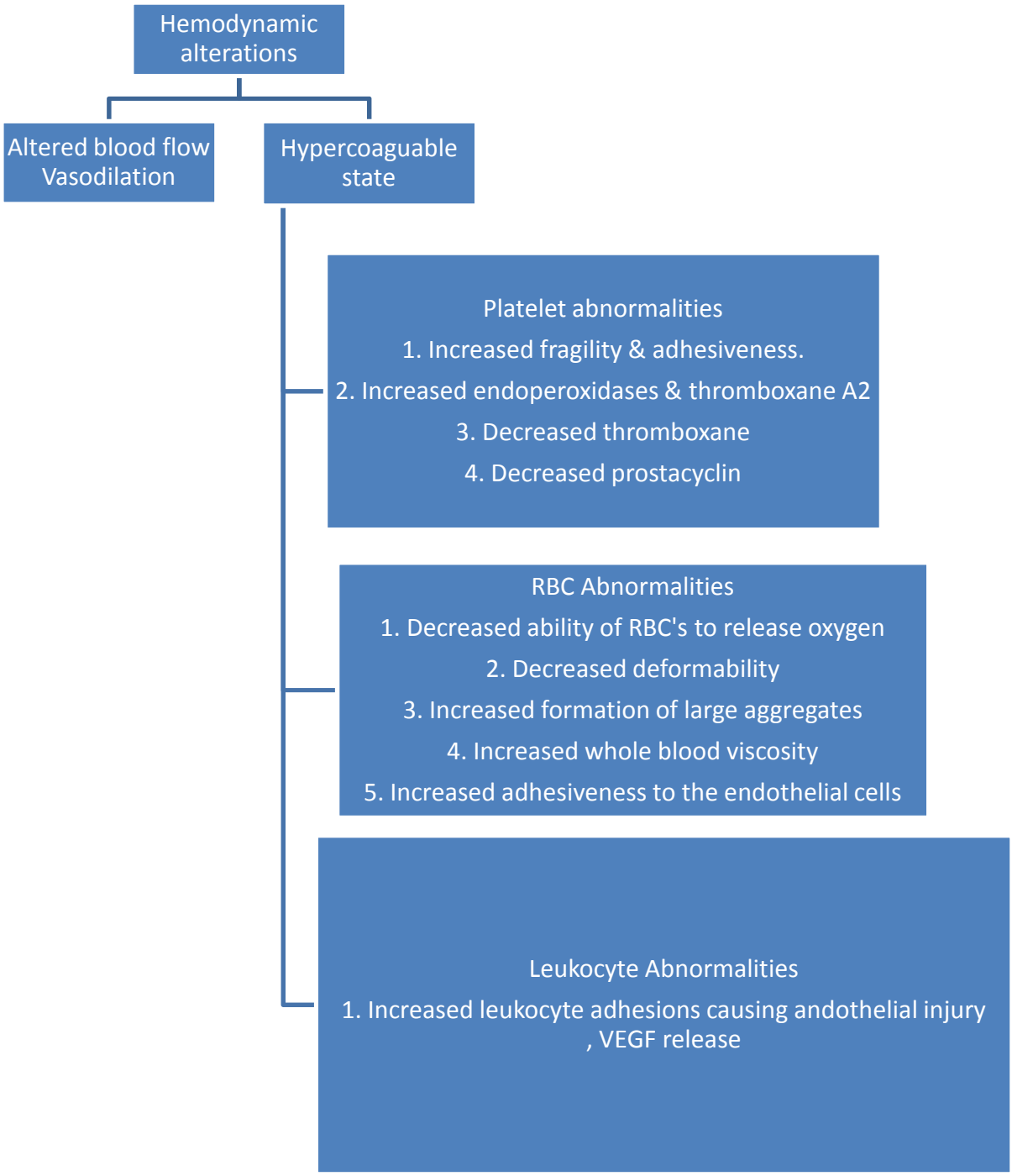
Epidemiology of Diabetic Retinopathy[2,3]

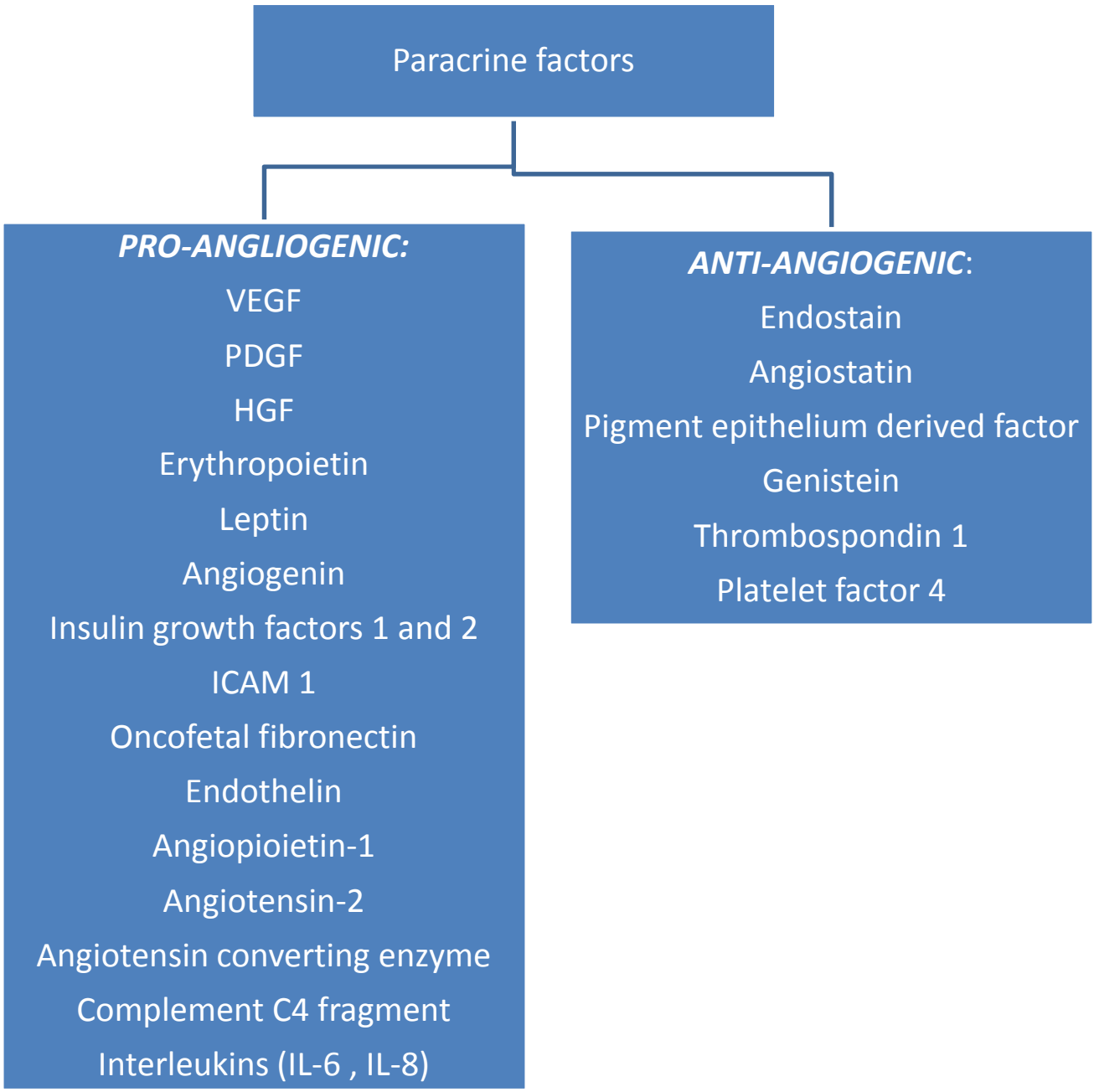
The large numbers of people affected with DR is an indication of the severity of the problem. Prevalence of Diabetic retinopathy was found to be 50.3% in USA[10], 33.6% in UK[55], 29.0% in Australia[54] and 17.6% in India[13].

Pathogenesis Of Diabetic Retinopathy [32,33,34]

The initiating factor which results in the structural changes of DR is hyperglycemia. Hyperglycemia induces these changes due to a combination of factors including biochemical, hemodynamic and paracrine factors producing structural changes in the vessels including (a) pericytes degeneration (b)basement membrane thickening and (c) endothelial cell proliferation.


Biochemical Alterations
Non-Enzymatic glycosylation and Advanced Glycation end products production
Increased polyol pathway flux
Protein kinase C Activation
Oxidative stress
Endothelial apoptosis VEGF production
Basement Membrane thickening
Induces / mediates action of VEGF
Oxygen free radicals damage enothelial cells


Hemodynamic alterations
Altered blood flow Vasodilation
Hypercoaguable state
Platelet abnormalities
1. Increased fragility & adhesiveness.
2. Increased endoperoxidases & thromboxane A2
3. Decreased thromboxane
4. Decreased prostacyclin
RBC Abnormalities
1. Decreased ability of RBC's to release oxygen
2. Decreased deformability
3. Increased formation of large aggregates
4. Increased whole blood viscosity
5. Increased adhesiveness to the endothelial cells
Leukocyte Abnormalities
1. Increased leukocyte adhesions causing andothelial injury , VEGF release


Paracrine factors
PRO-ANGLIOGENIC:
VEGF
PDGF
HGF
Erythropoietin
Leptin
Angiogenin
Insulin growth factors 1 and 2
ICAM 1
Oncofetal fibronectin
Endothelin
Angiopioietin-1
Angiotensin-2
Angiotensin converting enzyme
Complement C4 fragment
Interleukins (IL-6 , IL-8)
ANTI-ANGIOGENIC:
Endostain
Angiostatin
Pigment epithelium derived factor
Genistein
Thrombospondin 1
Platelet factor 4

Increase in lipid peroxides in blood coupled with weakness of defense antioxidant system in diabetics without complication probably serves as a background for pathogenesis of endothelial dysfunction associated with diabetes mellitus.[34]

CLASSIFICATION OF DIABETIC RETINOPATHY [35]

MODIFIED AIRLIE HOUSE CLASSIFICATION

ABBREVIATED ETDRS CLASSIFICATION:

CATEGORY DESCRIPTION	MANAGEMENT
NON-PROLIFERATIVE DIABETIC RETINOPATHY (NPDR)	
No DR	Review in 12 months
Very mild : Microaneurysms only	Review most patients in 12 months
Mild : Any or all of: Microaneurysms, retinal hemorrhages, exudates, cotton wool spots, up to the level of moderate NPDR. No IRMA or significant beading	Review range 6-12 months, depending on severity of signs, stability, systemic factors, patient's personal circumstances
Moderate: Severe retinal hemorrhages (more than ETDRS standard photograph 2A) Significant venous beading in no more than 1 quadrant Cotton wool spots commonly present	Review in approximately 6 months
Severe 4:2:1 rule : one or more of :	Review in 4 months

Severe hemorrhages in all 4 quadrants Significant venous beading in 2 or more quadrants Moderate IRMA in 1 or more quadrants	
Very Severe 2 or more of the criteria for severe	Review in 2-3 months
PROLIFERATIVE DIABETIC RETINOPATHY (PDR)	
MILD-MODERATE New vessels on disc (NVD) or new vessels elsewhere (NVE),but extent insufficient to meet high risk criteria	Treatment considered according to severity of signs, stability, systemic factors, patient's personal circumstances. If not treated, review in 2 months
HIGH RISK New vessels on disc (NVD) greater than ETDRS standard photograph 10A (about 1/3 disc area) Any NVD with vitreous or preretinal hemorrhage NVE greater than ½ disc area with vitreous or preretinal hemorrhage (or	Immediate treatment

hemorrhage with presumed obscured NVD/E)	
<u>Advanced diabetic eye disease</u> Tractional retinal detachment, significant persistent vitreous hemorrhage and neovascular glaucoma	Immediate treatment

CLINICAL FEATURES [5,32,33]

NON-PROLIFERATIVE DIABETIC RETINOPATHY

It is the most common form of diabetic retinopathy. Opthalmoscopically the following findings may be seen.

MICROANEURYSMS

They are caused by hypercellular out pouching of the capillary walls due to loss of pericytes. Mostly located within the inner nuclear layer,they appear as small red dots with sharp margins and are less than 1/12 the diameter of an average optic disc or 125u in its longest dimension. Their diameter varies between 12-100u, however only those greater than 30u can be visualized with direct ophthalmoscope. On fluorescein angiography ,these microaneurysms are seen as hyperfluorescent dots that fill during early venous phase and remain hyperfluoresent during the late phase without any change in size or others may become larger with leakage of dye in the surrounding tissue. Most of these are located in posterior pole with a predisposition for the area temporal to the fovea.

These microaneurysms undergo a thickening and hyalinization of the walls over a period of time resulting in “auto-occlusion” and they appear yellow or white in color. Most of the microaneurysms are present adjacent to the area of capillary non-perfusion (CNP) and as the area of CNP advances, these microaneurysms may disappear.

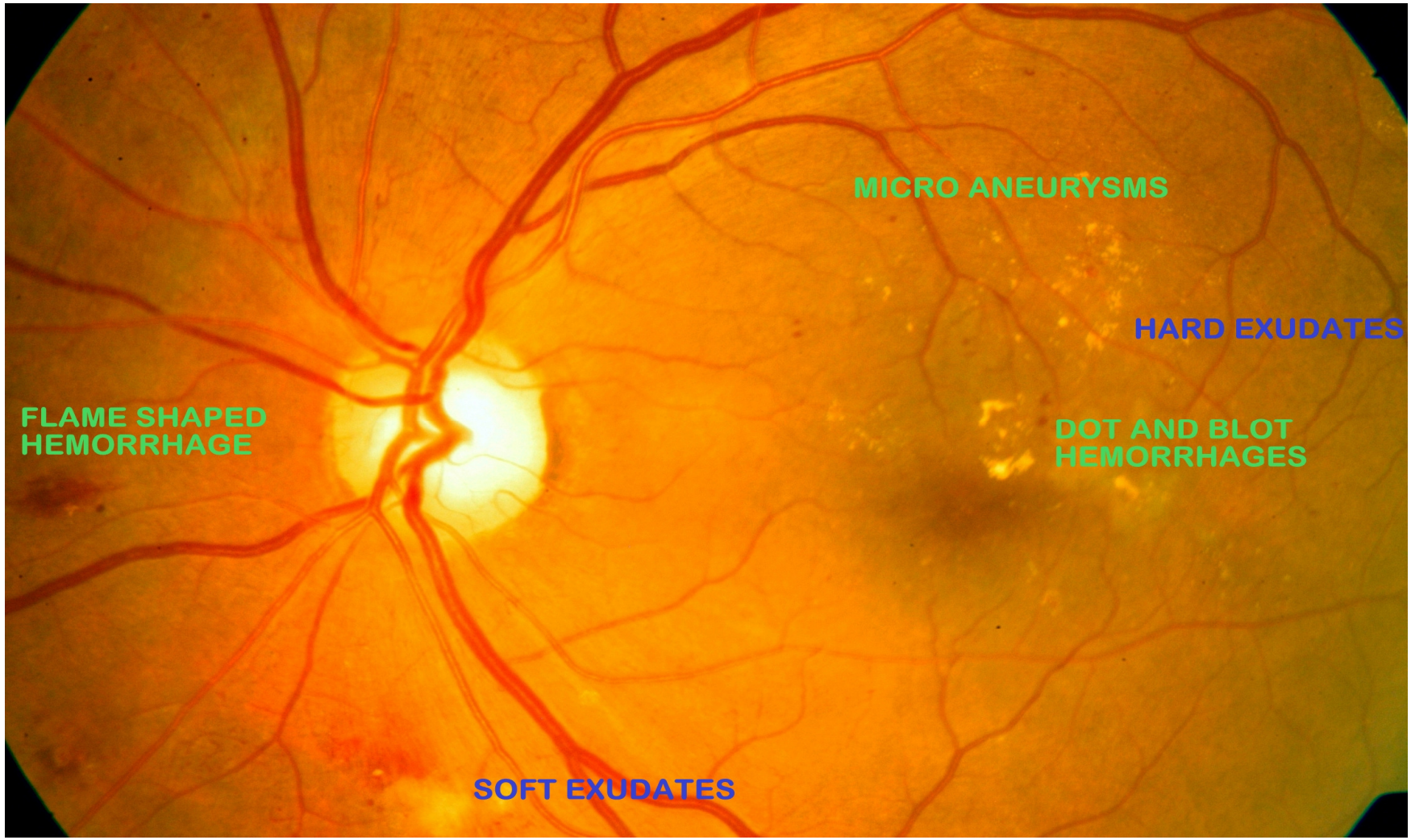


FIGURE 2: FUNDUS COLOR PHOTOGRAPH

RETINAL HEMORRHAGES

The wall of capillary or microaneurysm may rupture and cause intraretinal bleeds. These hemorrhages may be seen in the superficial or deep layers of retina and acquire specific shapes according to the situation. Those in superficial layers assume flame shape as the nerve fibers run parallel to the surface of the retina and are thus called flame shaped or splinter hemorrhages. They are the result of superficial capillary bleeds due to raised arterial pressure. They generally absorb in 3 months time.

In the deeper layers (outer plexiform and inner nuclear layers) the cells are arranged perpendicular to the retinal surface, therefore bleeding in this area are round or oval in shape and thus termed 'dot and blot' hemorrhages. They are usually more than 1/12 the diameter of an average optic disc or greater than 125u in its longest dimension and usually have irregular margins and/or uneven density. Their color depends on the oxygen contents, those with greater amounts of oxyhemogloblin appear red whereas those with lesser amounts appear darker. Fundus fluorescein angiography can be used to differentiate them from microaneurysms. Hemorrhages appear as hypofluorescent areas due to blocked fluorescence. Intraretinal hemorrhages cause visual disturbance only if located in foveolar region. Blot haemorrhages tend to appear in clusters indicating underlying capillary closure and therefore is an important indicator of progression of retinopathy.

HARD EXUDATES

These are actually lipid accumulations that leak from abnormal vessels. They appear as glistening, yellowish white in color with waxy appearance and sharp margins. Mostly located in outer plexiform layer, though they may be more superficial especially in presence of retinal edema. They may be scattered throughout the macula or accumulate in the form of circinate ring around the microaneurysms and such a pattern is referred to as “circinate retinopathy”. The circinate rings are seen at junction of abnormal and normal retina. These hard exudates get absorbed by phagocytosis and thus disappear over a period of months to years. The macrophages clearing these hard exudates migrate through the retina into adjacent normal capillaries.

COTTON WOOL SPOTS

Also known as soft exudates, they represent nerve fiber layer infarcts and are caused by occlusion of pre capillary arterioles that result in retinal axonal swelling due to accumulation of intracellular fluid or organelles secondary to impaired axoplasmic flow in the area of capillary non-perfusion. They appear round or oval with pale yellow-white or grayish-white color and less than half a disc diameter with fluffy appearance and feathery borders. On fluorescein angiography,they appear as areas of capillary non-perfusion, usually lined by microaneurysms. Their mean life is 3-17months and they disappear earlier in younger patients. Those associated with hypertension disappear earlier. On

resolution, the nerve fibers and ganglion cells of the inner retina become atrophic and depressed producing a “Depression sign”. There may be a transient increase in the number in patients who are initiated on insulin therapy and brought under tight metabolic control.

INTRARETINAL MICROVASCULAR ABNORMALITIES (IRMA)

These are narrow, tortuous intraretinal vascular segment that are thought to represent : (a) dilated capillaries that function as collateral channels during hypoxia or (b) new vessel growth within the retina. Their presence indicates severe form on NPDR with an impending risk of developing retinal neovascularisation.

Some differentiating features between IRMAs and preretinal new vessels include:

- Neovascularization tends to form a cart-wheel like network
- New vessels extend across both arterial and venous branches of underlying vessels
- New vessels may show accompanying fibrous proliferation
- Biomicroscopic retinal examination shows more superficial location of preretinal new vessels
- FFA shows profuse leakage from new vessels whereas IRMAs do not leak

VENOUS CHANGES

Severe retinal hypoxia and sluggish circulation results in venous caliber abnormalities characterized by venous dilatation, beading and loop formation. Transient dilatation of veins may be seen in hyperglycemia, even in the absence of any retinopathy and may represent a preclinical stage of diabetic retinopathy. The localized variation in venous caliber is typical of diabetic retinopathy and is designated as venous beading while the venous loops are hairpin or semicircular deviations of the vein from its normal course. On fluorescein angiography, there are areas of capillary non-perfusion adjacent to these venous changes, thus indicating ischemia.

FEATURELESS RETINA

In the late stage of the NPDR, larger arterioles may occlude completely resulting in extensive capillary non-perfusion. Retina may appear thin and atrophic and does not show any background lesions. This may result in underestimation of the actual severity of the disease. Careful evaluation has to be done for occluded arterioles and areas of avascular retina that is thinner and duller compared to healthy retina. Fluorescein angiography reveals extensive areas of capillary non-perfusion. This is an important sign as these patients may develop neovascularisation of iris and angle without showing any retinal vascularisation.

PROLIFERATIVE DIABETIC RETINOPATHY (PDR)

PDR is characterized by proliferation of new vessels on the optic disc (NVD) or elsewhere (NVE).It indicates more severe form of the disease reflecting marked underlying ischemia.The vascular bed adjacent to the area of new vessels dilates and may be a stimulus for new vessel formation.Both ischemia and a dilated capillary bed act as a trigger for initiating the process of angiogenesis.

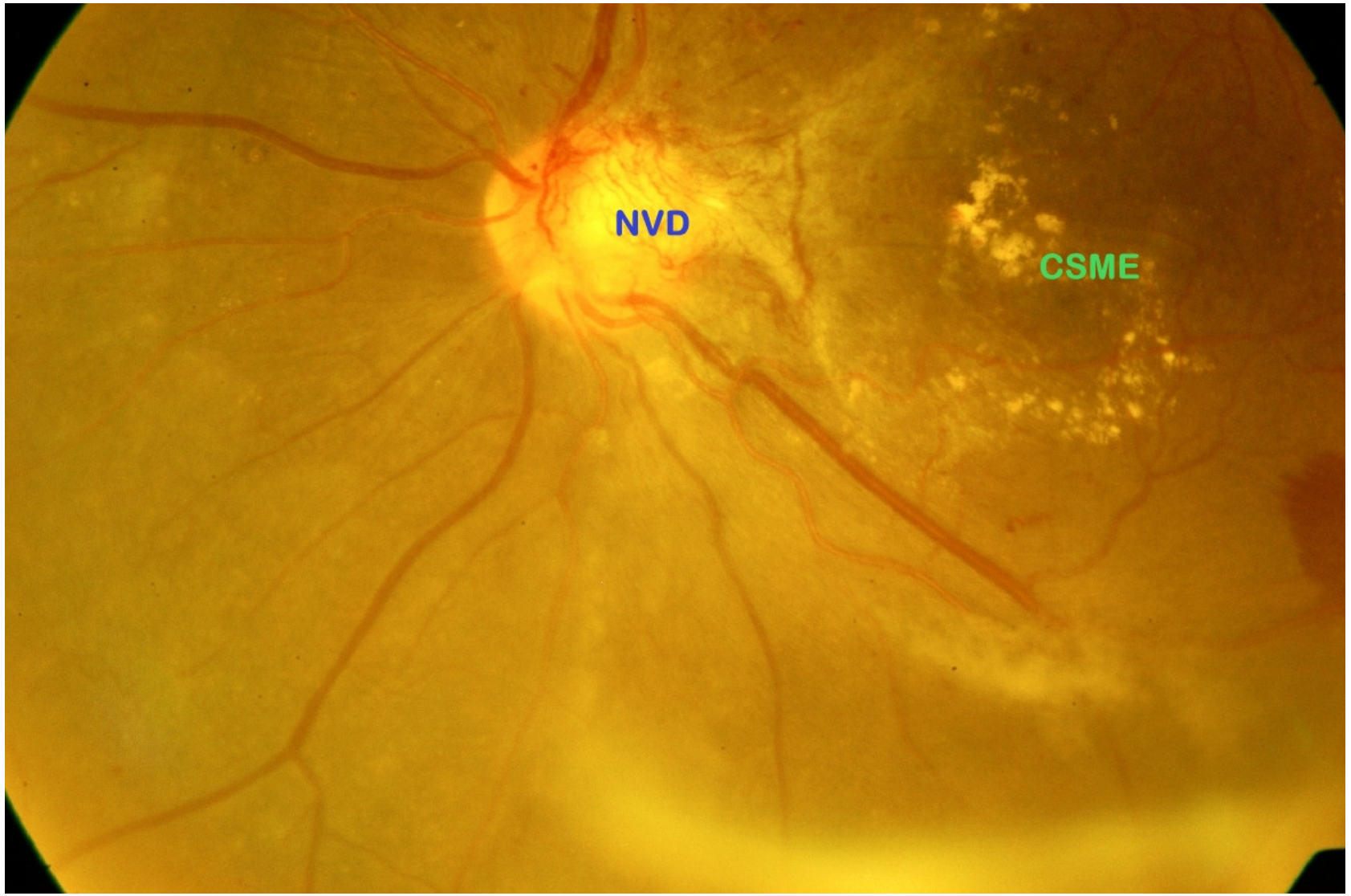


FIGURE 3: FUNDUS COLOR PHOTOGRAPH SHOWING NEOVASCULARISATION OF DISC

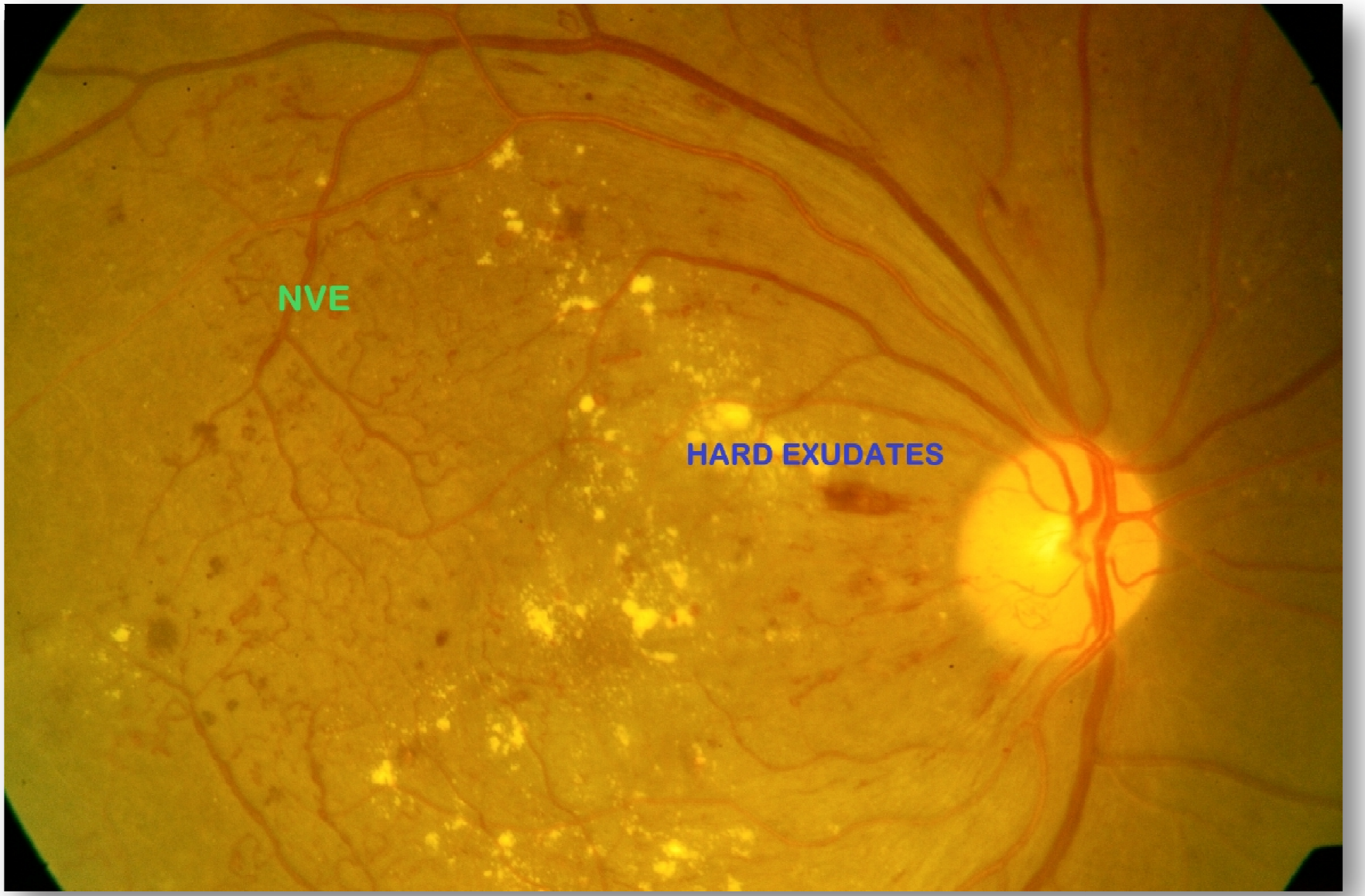


FIGURE 4: FUNDUS COLOR PHOTOGRAPH SHOWING NEOVASCULARISATION ELSEWHERE

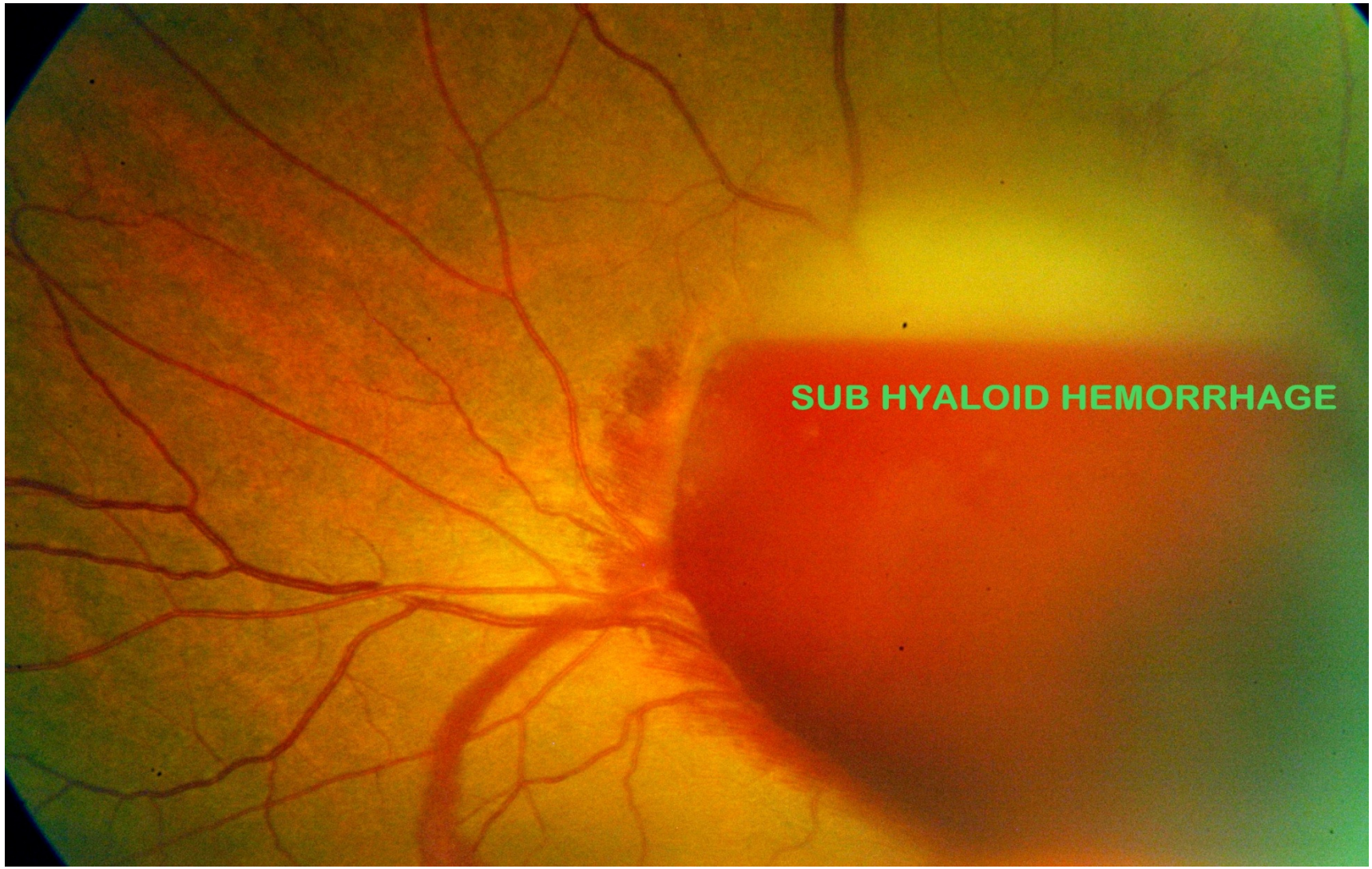


FIGURE 5: FUNDUS COLOR PHOTOGRAPH SHOWING SUBHYALOID HEMORRHAGE

METHODS OF RETINAL EXAMINATION [5,32,33]

Various methods can be used to evaluate retinal changes in diabetic retinopathy.

1.DIRECT OPHTHALMOSCOPY

Though an easy and convenient method, its two main disadvantages are the lack of a stereoscopic view of structural changes which are three dimensional by nature and the difficulty of recording and transmitting the information or of making any form of quantitative assessment of the disturbance.

2.INDIRECT OPHTHALMOSCOPY

This is more useful in patients with opacities in the ocular media. Good illumination and wide field of view make this the instrument of choice for examining retina in detail upto the periphery. Indentation will give view of the peripheral retina.

3.SLIT LAMP BIOMICROSCOPY

The fundus viewing contact lens allows examination of the posterior vitreous and posterior pole of the fundus with the slit lamp microscope. Goldmanns lens is commonly used and is a plano-concave contact lens. It is used during laser photocoagulation and during vitrectomy. The central zone of 3 mirror contact lens can also be used as a fundus viewing lens.

By 90D or 78D condensing lenses, the real image of the retina formed by the condensing lenses may be viewed through slit lamp microscope. The 90D lens gives a wider field of view but lesser magnification than the 78D lens. Though it gives an excellent view of the posterior pole of the fundus, it is less suitable

for examining the periphery of retina. It gives a stereoscopic view of the macula. The panfundoscopic contact lens gives a panoramic view of the retina.

4.FUNDUS PHOTOGRAPHY

Grading of retinopathy can be done with the help of fundus photographs and the progression or the effect of treatment can be assessed by serial photographs.

In this study I used the Zeiss FF450 Plus camera to take fundus photographs.

5.FLUORESCEIN ANGIOGRAPHY (FFA)

This allows us to examine structures in the retina which are beyond the limit of direct ophthalmoscopy and also enables the study of hemodynamic changes that occur in the retina and the localised abnormalities of flow and perfusion that are the background for many pathological disturbances.

Under normal circumstances the contrast medium fluorescein,does not leak out of the retinal vessels.Abnormal fluorescence in an angiogram may be due to:

(1) Hyperfluorescence

- Leakage of dye from microaneurysms, IRMA, new vessels and from damaged capillaries
- Leakage from optic nerve head in NVD
- Staining of tissues as a result of prolonged retention of fluorescein

(2) Hypofluorescence

- Blockage of fluorescence by increased density of pigment (xanthophyll), hard exudates and blood

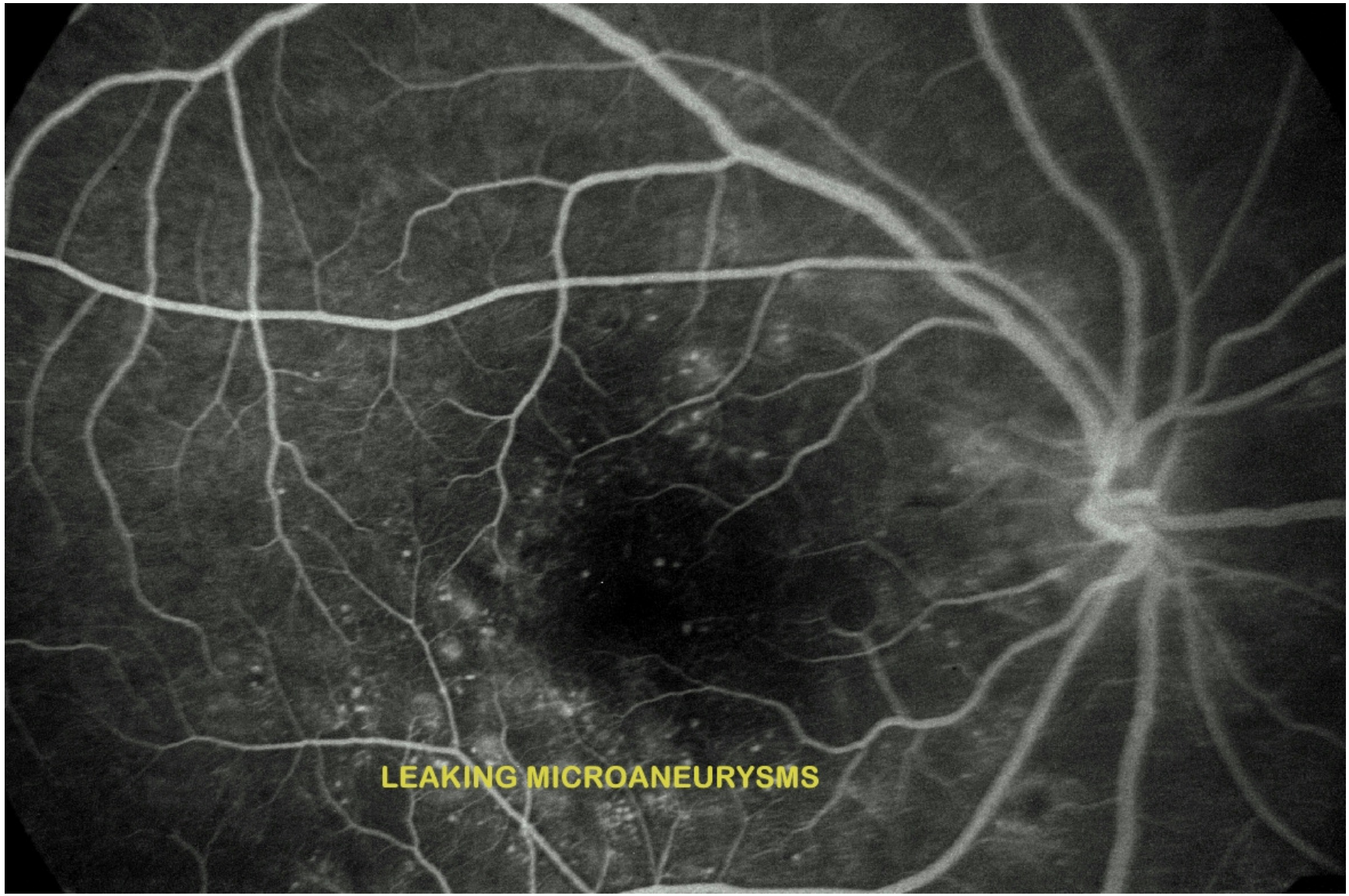


FIGURE 6 : FUNDUS FLUORESCEIN ANGIOGRAM

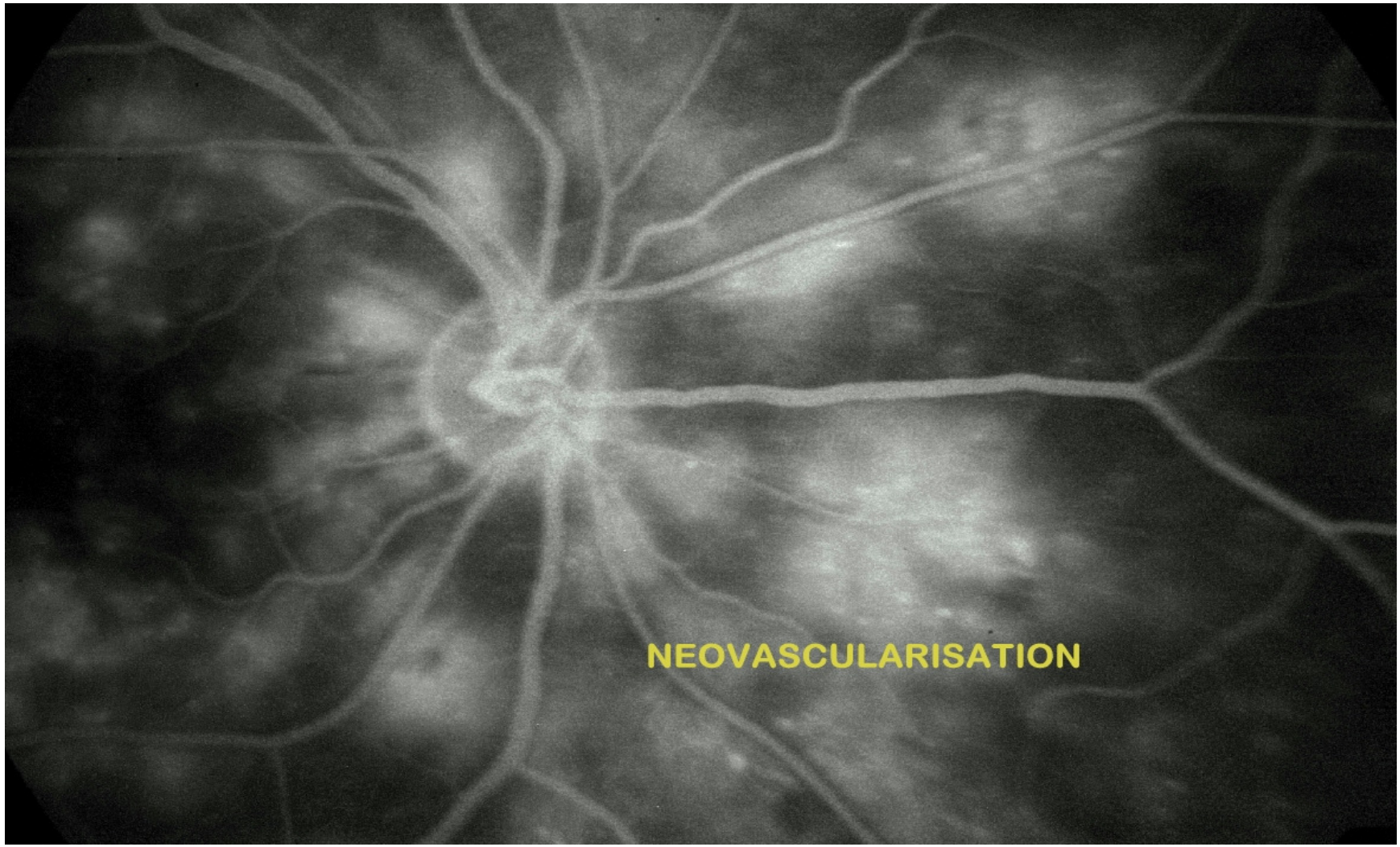


FIGURE 7 : FUNDUS FLUORESCEIN ANGIOGRAM

- Obstruction of circulation preventing access of fluorescein to the tissues resulting in areas of capillary nonperfusion. This is a very good indicator of retinal ischemia which will lead to development of neovascularisation.

FFA is an excellent method of showing retinal capillaries and a good guide for laser photocoagulation and to assess the effect of treatment.Neovascularisation elsewhere occurs usually at the junction of perfused and non-perfused retina and the most common location is along the temporal vascular arcades.[36]

5. ELECTRO DIAGNOSTIC TESTS (ERG)

It is the record of an action potential produced by the retina when it is stimulated by light of adequate intensity.

It is useful in assessing retinal function in diabetic retinopathy, when the media is opaque due to cataract or vitreous hemorrhage.

6. ULTRASOUND 'B' SCAN

In DR, it is used when the media is opaque to detect whether there is any vitreous hemorrhage, posterior vitreous detachment, traction or rhegmatogenous retinal detachment or to detect the presence of epiretinal membranes.

- Vitreous opacities produce dots or short lines.
- Membranous lesions produce an echogenic line.

7. VISUAL ACUITY

It is the most important test of macular function, particularly for near. Hypermetropia, with disparity between the subjective and objective refraction

of the eye, is characteristic of a shallow elevation of sensory retina at macula. In CSMO, near visual acuity is affected.

8. AMSLER GRID

Evaluates the 20 degrees of visual field surrounding fixation. It is primarily used for screening macular function.

9. PHOTOSRESS TEST

May be useful in demonstrating macular lesions when ophthalmoscopy is equivocal in early cystoid macular edema.

10. POTENTIAL ACUITY METER

This is done by projecting a standard Snellen's chart onto the macula through a small area of an immature cataract and asking the patient to read the letters.

TREATMENT OF DIABETIC RETINOPATHY [37,38]

First and a very essential step is control of diabetes.This is very important in preventing development of microvascular complications.The main modes of treatment of diabetes mellitus are:

1.INSULIN THERAPY

This is the mainstay in youth onset diabetes and maturity onset diabetes,in whom oral hypoglycaemic agents have failed to maintain satisfactory blood sugar levels.

Available insulin preparations are:

- Rapid acting preparations – for intravenous, intramuscular and subcutaneous use with peak activity of 2-4hrs.
- Intermediate acting preparations – such as NPH (Isophane) and Lente (Zinc) with a 6-12 hr span of peak activity.
- Long acting preparations – such as ultra lente and protamine zinc insulin (PZI) with 14-24 hrs span of maximal action.
- Human Insulin- synthetic insulin with a structure identical to that of human hormone has largely replaced animal insulins. It is produced either by chemical synthesis or by recombinant DNA techniques. It is less antigenic.

Regimen of meticulous control

- Intensified multiple subcutaneous insulin injections
- Continuous subcutaneous insulin infusion

- Implantable intraperitoneal pumps

Risk of meticulous control

Acceleration of diabetic retinopathy- though not a common complication, amelioration of severe retinopathy cannot be expected. According to DCCT study, the progression of early retinopathy slowed down.BDR is not a contraindication for meticulous control, but frequent ophthalmologic surveillance is required to detect accelerated neovascularisation. The reason for worsening is unknown. Perhaps retinal glucopenia may stimulate vascular endothelial growth factor (VEGF).VEGF receptors are present in endothelial cells of retina and of major vessels.

2.DIET THERAPY

Normal weight persons with diabetes usually require about 35kcal/kg body weight/day and 0.8-1gm protein/kg body wt/day. A standard recommendation is for fat content to be 30% or less of total calories and for saturated fat to be in the range of 7-10%.

3.EXERCISE

4.ORAL HYPOGLYCEMIC AGENTS

- SULPHONYL UREAS –Glipizide, Glimepride, Glyburide
- BIGUANIDES – Metformin

- MEGLITINIDES – Nateglinide, Repaglinide
- THIAZOLIDINEDIONES – Pioglitazone, Rosiglitazone
- α – GLUCOSIDASE INHIBITORS – Acarbose, Miglitol
- DPP-IV INHIBITORS - Sitagliptin

SPECIFIC TREATMENT FOR DIABETIC RETINOPATHY

- Laser Photocoagulation
- Surgical – Vitrectomy, Intravitreal Injections

LASER PHOTOCOAGULATION

It is recommended that patients with severe and very severe NPDR must receive laser treatment when exposed to several risk factors that can influence progression of disease.

Risk factors for laser treatment[39]:

NON-MODIFIABLE	Diabetes Mellitus type I Opposite eye with PDR Extensive zones of capillary closure on FFA
MODIFIABLE	Glycemic control Elevated serum lipids Hypertension Renal dysfunction
TIMEABLE	Pregnancy Cataract in evolution Strict glycemic control Irregular followup

Macular photocoagulation for CSME are of two types [5,36]:

1.Focal – for leaking microaneurysm

2.Grid – for diffuse macular edema

Since the visual outcome following grid laser is poor, surgical intervention is preferred instead. Focal laser for CSME should precede Pan retinal photocoagulation by 6-8 weeks ideally.

Panretinal photocoagulation is usually done in 2 or more sessions to prevent macular edema. In the first session, inferior quadrants are done and in the

second session, the superior quadrants and also open macular closure are done. More sessions may be added if required.

ETDRS RESEARCH GROUP PROTOCOL FOR PRP[40]	
Spot size	500microns
Exposure time	0.1s
Intensity	Moderate
Number of shots	1200 – 1600
Location	Diameter of shot separation, >2DD out of fovea to the equator
Number of sessions	At least 2
Treated lesions directly	New vessels 2DD extrapapillary
Indications for new treatment	Areas of new vessels extrapapillary, high risk PDR, recurrence

SURGICAL THERAPY

Pars Plana Vitrectomy:

Current indications for vitrectomy in diabetic eye disease[41]

• Severe non-clearing vitreous hemorrhage.

• Tractional retinal detachment involving macula

• Combined tractional and rhegmatogenous detachment

• Severe progressive fibrovascular proliferation

• Dense pre-macular hemorrhage

• Macular edema associated with or without posterior hyaloid traction

• Diffuse macular edema with massive hard exudates

• Ghost cell glaucoma

• Anterior hyaloidal fibrovascular proliferation

• Fibrinoid syndrome with associated retinal detachment.

The diabetic retinopathy vitrectomy study (DRVS) demonstrated that early vitrectomy (1-4 months after onset of severe vitreous hemorrhage cause <5/200 vision) resulted in a slightly higher proportion of cases achieving a final vision of ≥20/40. The difference was more marked for the subgroup of patients with Type-I DM, indicating that the optimal timing for vitrectomy in severe vitreous hemorrhage in type I diabetes is sooner, around 3 months after onset.[42]

Vitrectomy with Internal Limiting membrane peeling at macula in cases of diabetic macular edema is done with the main objective being relieving the traction of ILM on macular area leaving retinal tissue force to settle and absorb the edema.[43,44] Prompt, rather than early vitrectomy, is indicated in a subgroup of patients characterized by presence of a dense pre-retinal hemorrhage confined within an incomplete PVD overlying the area centralis.[45]

Intravitreal Injections:

Intravitreal Triamcinolone acetonide (IVTA) during vitrectomy or given alone is reported to cause short term regression of diabetic macular edema and increase visual acuity. IVTA after 6 months or less leads to prolonged beneficial improvement of vision.[46,47] Posurdex is a biodegradable, extended-release dexamethasone implant that has shown promising outcomes in the treatment of macular edema of various etiologies including diabetic macular edema.[48]

Anti-VEGF antibodies like Bevacizumab (Avastin), Pegaptanib (Macugen), Ranibizumab (Lucentis) are widely used nowadays for the treatment of neovascularisation in DR.

VEGF is produced by pericytes, the pigment epithelial cells, and endothelial cells of the retina in response to hypoxia from capillary loss and/or microaneurysm formation. Clinical studies have shown that intravitreal VEGF

concentration increased in eyes as they progressed from nonproliferative diabetic retinopathy to active proliferative diabetic retinopathy [49].

Protein Kinase C (Pkc) Inhibitors like LY333531 (ruboxistaurin, RBX) and PKC412 (midostaurin) are currently being studied for the treatment of DR. [50,51]

Octreotide (a somatostatin analog) and Sandostatin (growth hormone/insulin-like growth factor-1 antagonist) decreased the need for retinal photocoagulation compared with conventional treatment in a study .[52]

OVERVIEW OF LIPIDS

The word cholesterol is derived from Greek words, 'chole'-bile and 'steros'-solid, 'ol'- alcohol.

LDL transports cholesterol from liver to peripheral tissues and is thus called 'bad cholesterol'.75% of plasma cholesterol is incorporated into LDL particles.HDL transports cholesterol from peripheral tissues to liver (reverse cholesterol transport) and so called 'good cholesterol'.

NCEP-ATP GUIDELINES III ON CLASSIFICATION OF LIPIDS[53]

LDL	<100 100-129 130-159 160-189 >= 190	Optimal Near/above Optimal Borderline high High Very High
CHOLESTEROL	<200 200-239 >= 240	Desirable Borderline high High
HDL	<40 >= 60	Low High

PART II

AIM

AIM OF THE STUDY

Primary Aim: To study association between serum lipid levels & severity of Diabetic retinopathy

Secondary Aims:

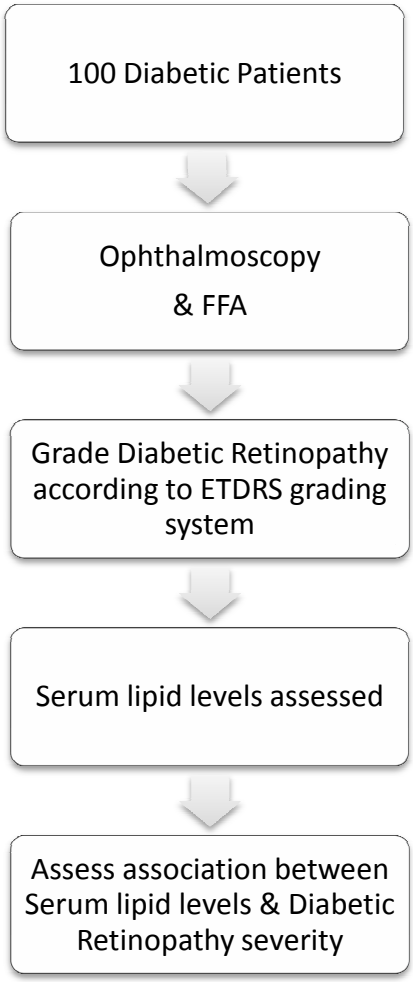
1. To assess the proportion of patients with dyslipidemia among patients with diabetic retinopathy

2. To assess association between various types of lipoproteins with diabetic retinopathy

MATERIALS AND METHODS

MATERIALS AND METHODS

- This is a prospective observational study conducted among patients attending Ophthalmology OPD in PSG Institute of Medical Sciences and Research Centre,Coimbatore.
- It is a cross-sectional,hospital based study spanning over a period of 18 months from June 2011 to November 2012.
- **Study design**



- **Inclusion criteria:**

  Type II Diabetes Mellitus

  Age >40yrs

  Either sex

  Duration of Diabetes 5-15years

- **Exclusion criteria:**

  Hazy media like Corneal opacity,Cataract, Vitreous hemorrhage

  Already existing retinal diseases other than diabetic retinopathy

  Factors that retard progression of DR-High myopia,advanced glaucoma

  Factors that accelerate the progression of DR- Severe anemia,renal disease,hypertension

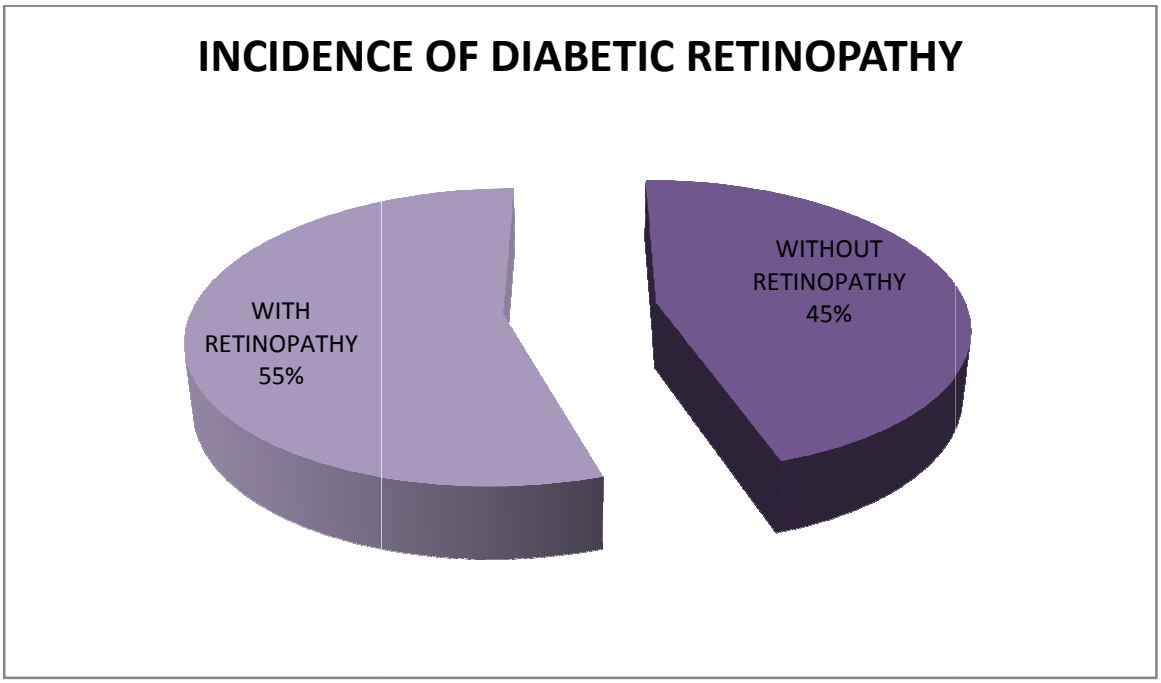
- 100 patients fitting into the inclusion and exclusion criteria were selected and a complete ophthalmological examination was done at presentation and included ophthalmoscopy and Fundus Fluorescein Angiogram.
- Their retinopathy status was then graded according to the ETDRS Grading System.
- Blood was collected and estimation of FBS, Lipid profile, Hb, Creatinine, HbA1C was done.
- The data collected was then analysed using SPSS software.

OBSERVATION & RESULTS

OBSERVATION AND RESULT

INCIDENCE

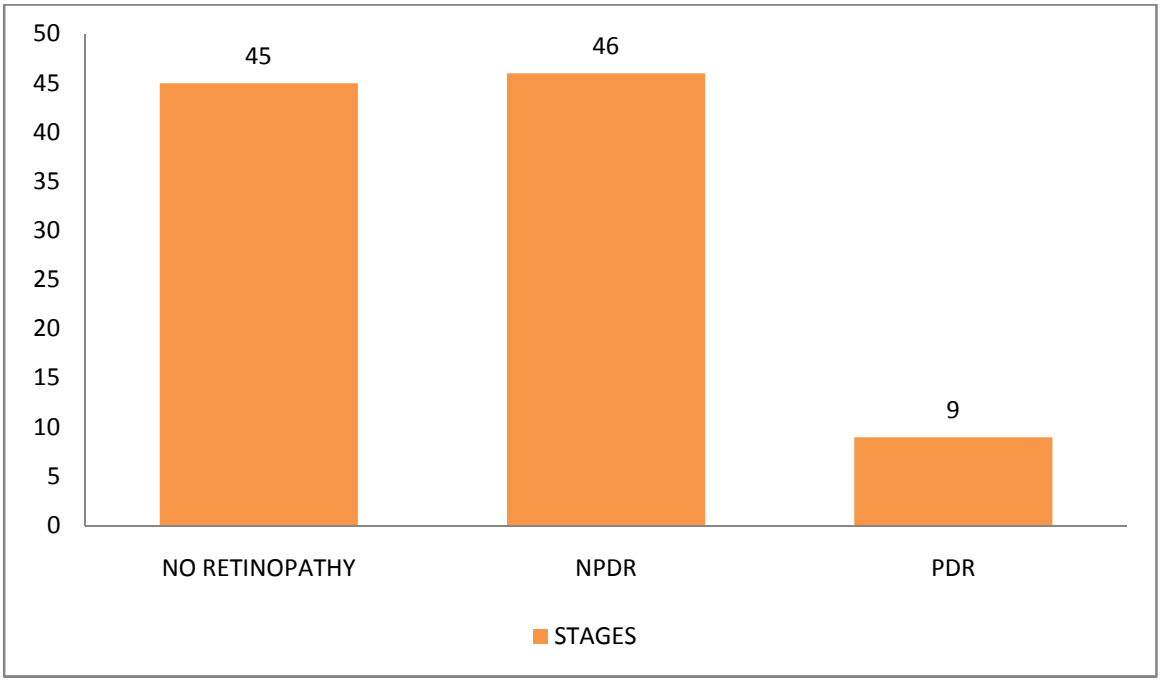
	DM WITHOUT RETINOPATHY	DM WITH RETINOPATHY
NO. OF CASES	45	55
PERCENTAGE	45%	55%



In our study the incidence of diabetic retinopathy was 55% and 45% had no features of diabetic retinopathy.

STAGING OF DIABETIC RETINOPATHY

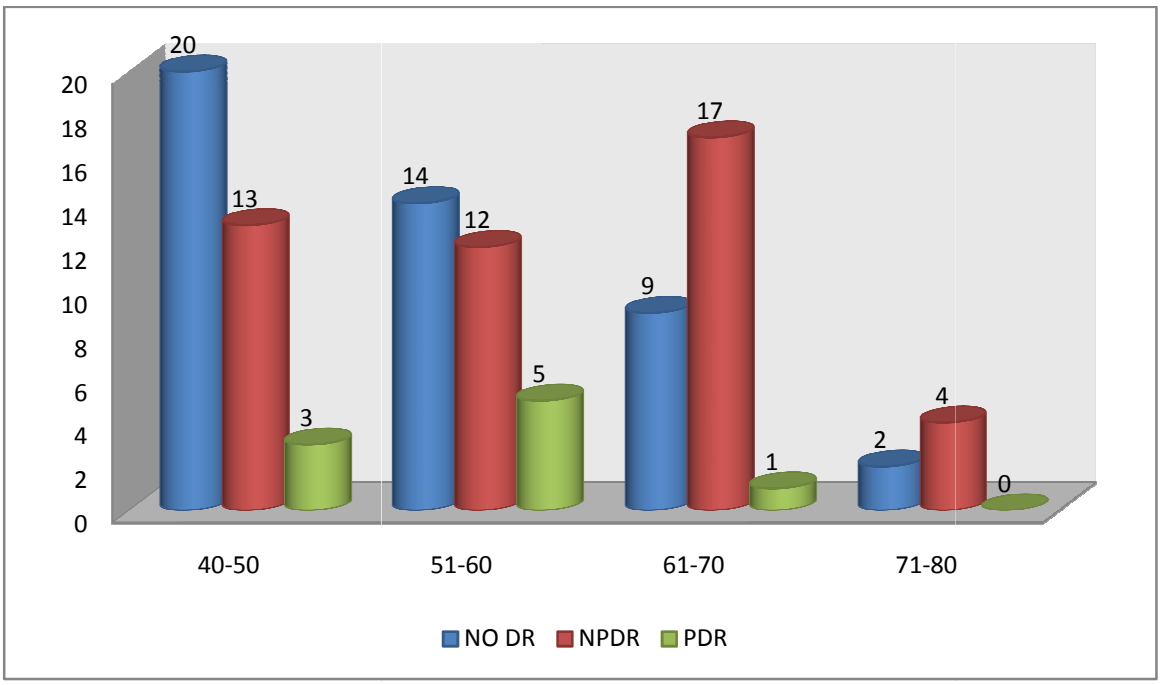
	NO DR	NPDR	PDR
NO. OF CASES	45	46	9
PERCENTAGE	45%	46%	9%



In our study, 45% had no signs of diabetic retinopathy, 46% had non-proliferative retinopathy and 9% had proliferative retinopathy.

AGE DISTRIBUTION

AGE IN YEARS	NO RETINOPATHY	NPDR	PDR	TOTAL
40-50	20	13	3	**36**
51-60	14	12	5	**31**
61-70	9	17	1	**27**
71-80	2	4	0	**6**
TOTAL	**45**	**46**	**9**	**100**

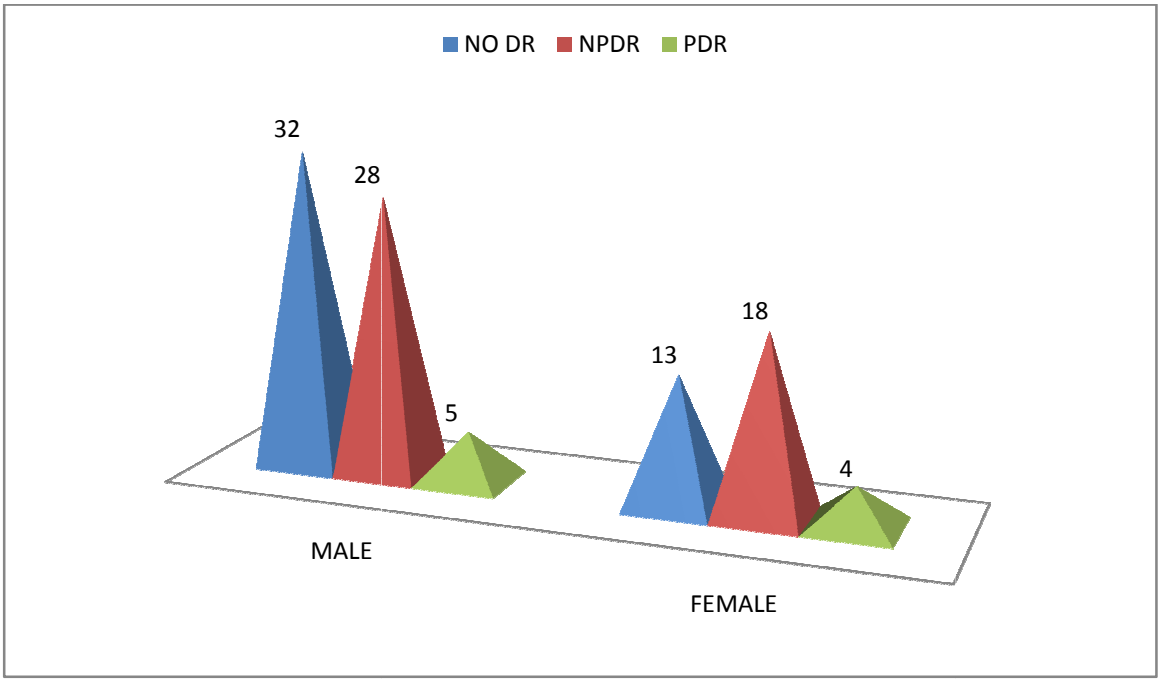


Mean age in the no diabetic retinopathy group was 54.02,in NPDR group it was 57.56 and in the PDR group it was 55.55.There was no significant association

between increasing age and diabetic retinopathy status according to this study (p-value 0.195).

SEX DISTRIBUTION

SEX	NO DR	NPDR	PDR	TOTAL
MALE	32	28	5	**65**
FEMALE	13	18	4	**35**
TOTAL	**45**	**46**	**9**	**100**



Of the 100 consecutive patients included in the study,65 were male and 35 female.In all 3 groups males predominated but in the PDR group the sex ratio was smaller as 5 of the PDR cases were males and the other 4 were females.

TOTAL CHOLESTEROL

	No DR	**NPDR**	**PDR**
MEAN	**177.22**	**186.86**	**159.33**
STANDARD DEVIATION	**41.15**	**52.12**	**47.74**
P VALUE	**0.24**		

According to our study,the mean total cholesterol levels are 177.22 in diabetics without retinopathy, 186.86 in NPDR and 159.33 in PDR.However since the p value is 0.24, there was no significance found with serum cholesterol levels and severity of diabetic retinopathy.

CHOLESTEROL LEVELS IN RETINOPATHY PATIENTS

		RETINOPATHY		TOTAL
		NPDR	PDR	
NCEP-ATP classification of CHOLESTEROL	<200 (Desirable)	27	8	35 (63.6%)
	200-239 (Borderline high)	13	0	13 (23.6%)
	≥240 (High)	6	1	7 (12.7%)
TOTAL		46	9	55

20 of the 55 patients (36.3%) with retinopathy had elevated serum total cholesterol levels.63.6% of retinopathy patients had desirable cholesterol levels.

TRIGLYCERIDES

	No DR	NPDR	PDR
MEAN	**141.97**	**163.13**	**195.00**
STANDARD DEVIATION	**68.87**	**86.05**	**192.50**
P VALUE	**0.243**		

The mean triglyceride levels were calculated as 141.97 in diabetics without diabetic retinopathy, 163.13 in NPDR and 195.00 in PDR patients.There was no significant association between serum triglyceride levels and severity of diabetic retinopathy with p value being 0.24.

HDL

	No DR	NPDR	PDR
MEAN	**39.73**	**36.80**	**31.66**
STANDARD DEVIATION	**15.01**	**10.32**	**12.43**
P VALUE	**0.19**		

The mean HDL values were 39.73 in diabetics without diabetic retinopathy, 36.80 in NPDR and 31.66 in PDR.Again there was no significant correlation between serum HDL levels and diabetic retinopathy severity (p-value 0.19).

HDL LEVELS IN RETINOPATHY PATIENTS

		RETINOPATHY		TOTAL
		NPDR	PDR	
NCEP-ATP classification of HDL	<40 (Low)	32	7	39 (70.9%)
	40-59	12	2	14 (25.4%)
	≥60 (High)	2	0	2 (3.6%)
TOTAL		46	9	55

39 of 55 (70.9%) retinopathy patients had low HDL levels and only 2 (3.6%) had high HDL levels which is desirable.

LDL

	No DR	**NPDR**	**PDR**
MEAN	**113.13**	**116.04**	**99.33**
STANDARD DEVIATION	**40.10**	**47.87**	**42.24**
P VALUE	**0.58**		

Mean LDL levels in diabetics without diabetic retinopathy was 113.13, 116.04 in NPDR and 99.33 in PDR.There was no significant correlation between serum LDL levels and severity of diabetic retinopathy (p-value 0.58).

LDL LEVELS IN RETINOPATHY PATIENTS

		RETINOPATHY		TOTAL
		NPDR	PDR	
NCEP-ATP classification of LDL	<100 (Optimal)	18	4	22 (40%)
	100-129 (Near optimal)	13	2	15 (27.3%)
	130-159 (Borderline High)	10	3	13 (23.6%)
	160-189 (High)	0	0	0 (0%)
	≥190 (Very high)	5	0	5 (9%)
TOTAL		46	9	55

22 of 55 retinopathy cases (40%) had optimal levels of LDL.Very high levels were seen only in NPDR cases in our study.

HBA1C

	No DR	NPDR	PDR
MEAN	**8.12**	**8.74**	**10.00**
STANDARD DEVIATION	**1.95**	**2.02**	**2.11**
P VALUE	**0.03**		

Mean glycosylated haemoglobin level was 8.12 in diabetics without retinopathy, 8.74 in NPDR AND 10.00 in PDR . There was significant correlation between glycosylated haemoglobin levels and staging of diabetic retinopathy (0.03).

FASTING BLOOD GLUCOSE

	No DR	NPDR	PDR
MEAN	**154.22**	**169.63**	**191.11**
STANDARD DEVIATION	**60.27**	**79.76**	**81.03**
P VALUE	**0.30**		

Mean Fasting blood glucose level was 154.22 in diabetics without retinopathy, 169.63 in NPDR and 191.11 in PDR.There was no significant correlation found between fasting blood glucose levels and severity of diabetic retinopathy (p value 0.30).

CREATININE

	No DR	NPDR	PDR
MEAN	**0.75**	**0.80**	**0.86**
STANDARD DEVIATION	**0.17**	**0.17**	**0.20**
P VALUE	**0.16**		

Mean creatinine level was 0.75 in diabetics without retinopathy, 0.80 in NPDR and 0.86 in PDR.There was no significant correlation found between serum creatinine levels and diabetic retinopathy (p-value 0.16).

HEMOGLOBIN

	No DR	NPDR	PDR
MEAN	**13.33**	**13.17**	**11.87**
STANDARD DEVIATION	**1.59**	**1.57**	**2.16**
P VALUE	**0.05**		

Mean serum haemoglobin is 13.33 in diabetics without retinopathy, 13.17 in NPDR and 11.87 in PDR.There was significant association with anemia and severity of diabetic retinopathy with p-value 0.05.

DISCUSSION

DISCUSSION

Of the 100 Type 2 diabetic patients included in this study, diabetic retinopathy was detected in 55%.The results are consistent with the Wisconsin Epidemiological Study for Diabetic Retinopathy conducted in the USA among 1313 subjects where 50.3% had diabetic retinopathy. However WESDR study was conducted among type I diabetics.[10]

In the Blue Mountain Eye Study (BMES)[54] conducted in Australia and the Liverpool Diabetic Eye Study[55] conducted in the United Kingdom, the prevalence of diabetic retinopathy was 29% and 33.6% each.

In the Chennai Urban Rural Epidemiological Study I (CURES I) which is an ongoing study conducted in India the prevalence of diabetic retinopathy in the 1715 subjects was 17.6% which is considerably lower than the above studies conducted in Western countries.[13]

In this study mean age in the no diabetic retinopathy group was 54.02,in NPDR group it was 57.56 and in the PDR group it was 55.55.There was no significant association between increasing age and diabetic retinopathy status according to this study (p-value 0.195).

Of the 100 consecutive diabetic patients included in our study, 65 were male and 35 were female. In all 3 groups males predominated but in the PDR

group the sex ratio was smaller as 5 of the PDR cases were males and the other 4 were females. According to CURES[13], UKPDS[56] and Hyderabad Study[57] males were affected more.

According to our study, the mean total cholesterol levels are 177.22 in diabetics without retinopathy, 186.86 in NPDR and 159.33 in PDR. However since the p-value is 0.24, there was no significant association found between serum lipid levels and severity of diabetic retinopathy. 20 of the 55 patients with retinopathy (36.3%) had elevated serum total cholesterol levels and 63.6% of retinopathy patients had desirable cholesterol levels.

The mean triglyceride levels were calculated as 141.97 in diabetics without diabetic retinopathy, 163.13 in NPDR and 195.00 in PDR patients. There was no significant association between serum triglyceride levels and severity of diabetic retinopathy with p value being 0.24.

The mean HDL values were 39.73 in diabetics without diabetic retinopathy, 36.80 in NPDR and 31.66 in PDR. Again there was no significant association between serum HDL levels and diabetic retinopathy severity (p-value 0.19). 39 of 55 (70.9%) retinopathy patients had low HDL levels and only 2 (3.6%) had high HDL levels which is desirable.

Mean LDL levels in diabetics without diabetic retinopathy was 113.13, 116.04 in NPDR and 99.33 in PDR. There was no significant association

between serum LDL levels and severity of diabetic retinopathy (p-value 0.58). 22 of 55 retinopathy cases (40%) had optimal levels of LDL. Very high levels were seen only in NPDR cases in our study.

The lower levels of total cholesterol and LDL in the PDR group in our study could be attributed to the increased awareness of their medical condition and thus more vigorous measures to achieve control of blood parameters in that group.

ETDRS report 22 states that those diabetics with increased total cholesterol, LDL or Triglyceride levels are more likely to have or develop retinal hard exudates, which can be associated with risk of vision loss, independent of the extent of macular edema. They also stated that the risk was twofold in cases with elevated serum LDL-c and total cholesterol levels[17].Klein et al inferred that this relationship was not applicable to type 2 diabetics that did not use insulin, and was seen in type 1 diabetics only[18]. This is consistent with our study which was conducted on type 2 diabetics.

Dhir, Dahiya et al conducted a study in North India and concluded that though the cholesterol profile values were slightly elevated in the diabetic retinopathy group, there was no significant difference noted.[58]

Mohan R, Mohan V, Susheela L, Ramachadran A, Viswanathan M et al concluded that the mean serum total cholesterol and LDL levels and also the

mean total/HDL cholesterol and mean LDL/HDL cholesterol ratios were significantly increased in diabetic maculopathy group as compared to the no retinopathy group. It was also reported that the mean serum HDL and VLDL cholesterol and the triglyceride levels were similar in both groups.[59]

Lyons TJ, Jenkins AJ, Zheng D, Lackland DT, McGee D, Garvey WT, Klein RL reported in 2004 that severity of retinopathy was positively associated with triglycerides and negatively associated with HDL cholesterol in type 1 diabetics.[19]

Rema et al in 2005 showed association of diabetic retinopathy with total cholesterol and serum triglycerides and also that diabetic macular edema showed a strong correlation with high LDL levels.[20]

Gupta A, Gupta V, Thapar S, Bhansali A conducted a randomized controlled trial on the role of atorvastatin in diabetic maculopathy and concluded that there was a decrease in the visible retinal lipid exudates and also a positive effect on the visual outcome of affected patients. They also confirmed that exudates may reduce or resorb within weeks of starting statin treatment and even before or without the need for argon laser photocoagulation.[21]

FIELD study showed a 30% reduction in laser interventions required in type 2 diabetic patients receiving fenofibrate, which reduces the serum lipid levels, versus the placebo group.[22]

Mean glycosylated haemoglobin level was 8.12 in diabetics without retinopathy, 8.74 in NPDR AND 10.00 in PDR . There was significant association between glycosylated haemoglobin levels and staging of diabetic retinopathy (0.03).

Mean Fasting blood glucose level was 154.22 in diabetics without retinopathy, 169.63 in NPDR and 191.11 in PDR. There was no significant association found between fasting blood glucose levels and severity of diabetic retinopathy (p value 0.30).

The CURES[6] and WESDR[10] all report that the level of hyperglycemia influences the development and progression of diabetic retinopathy. The WESDR and DCCT[6] studies in type 1 and UKPDS[56] study in type 2 showed protective role of glycemic control in prevention and non-progression of diabetic retinopathy. In the CURES Eye Study, for every 2% elevation of HbA1c level, the risk of diabetic retinopathy increased by a factor of 1.7 and in the UKPDS study, for every 1% reduction of HbA1c, the risk reduction in eye complications was 19%.

The phenomenon of ongoing beneficial effects on diabetic complications after a period of improved glycemic control even if followed by a return to usual (often poorer) metabolic control, has been described as representing "metabolic memory" by the DCCT/EDIC investigators[7] and as a "legacy effect" by the UKPDS investigators[8].Early insulinisation has been recommended by

Ranjit Unnikrishnan I, Anjana RM, Mohan V based on the above concepts[9].This shows the importance of long term control of blood sugar which is also proved in our study.

Mean creatinine level was 0.75 in diabetics without retinopathy, 0.80 in NPDR and 0.86 in PDR.There was no significant association found between serum creatinine levels and diabetic retinopathy (p-value 0.16).

Several studies have demonstrated association between nephropathy and diabetic retinopathy though they have mainly focused on the albuminuria and proteinuria levels. We however have considered serum creatinine in our study and excluded all those with elevated serum creatinine levels. Proteinuria was reported in 29.2% of DR patients in the CURES Eye Study[60]. WESDR[10] also showed association between microalbuminuria and Mohan et al reported that PDR was more prevalent in macroproteinuria than in microproteinuria[27].

Mean serum haemoglobin is 13.33 in diabetics without retinopathy, 13.17 in NPDR and 11.87 in PDR.There was significant negative association with haemoglobin levels and severity of diabetic retinopathy with p-value 0.05.

Anemia is a known risk factor for diabetic retinopathy and the reason suggested is the availability of smaller amounts of oxygen for the retinal tissue. Spontaneous closure of microaneurysms has been reported by Singh et al on correction of anemia and metabolic control in type 1 diabetics[61]. ETDRS also

reported low hematocrit as an independent risk factor for high risk PDR development and visual impairment[26]. Qiao Q et al reported a fivefold risk of diabetic retinopathy severity in patients with low hemoglobin levels. In our study we have excluded patients with anemia.[62]

NEED FOR THE STUDY

The need for such a study is because of the conflicting results seen in the older studies on the association between diabetic retinopathy and lipid levels. Our study mainly focuses on the South Indian population and thus reducing the errors due to changes in ethnicity. If there is a significant role of lipid levels in diabetic retinopathy, control of the former could be beneficial for the latter. The role of lipid level control in the prevention and retardation of progress of DR in our population is also assessed in our study.

LIMITATIONS OF THE STUDY

The drawback of our study is the limitation of the study group size as it does not portray a large proportion of the population. Since only those patients attending the Ophthalmology OPD are included in the study,all those who did not seek medical attention have been missed.

CONCLUSION

CONCLUSION

1. Diabetic retinopathy was detected in 55%.
2. In our study, 45% had no signs of diabetic retinopathy, 46% had non-proliferative retinopathy and 9% had proliferative retinopathy.
3. No significant association between increasing age and diabetic retinopathy status is seen.
4. Of the 100 consecutive diabetic patients included in the study,65 were males and 35 were females.In all 3 groups males predominated in this study with a decreased male:female ratio in the PDR group.
5. No significance was found with total serum cholesterol levels and severity of diabetic retinopathy.
6. 36.3% of patients with retinopathy had elevated serum total cholesterol levels.
7. There was no significant association between serum triglyceride levels and severity of diabetic retinopathy.
8. Again there was no significant association between serum HDL levels and diabetic retinopathy severity.
9. 70.9% of retinopathy patients had low HDL.
10. There was no significant association between serum LDL levels and severity of diabetic retinopathy.
11. 60% of retinopathy cases had elevated LDL levels.

12. There was significant association between glycosylated haemoglobin levels and staging of diabetic retinopathy.
13. There was no significant association found between fasting blood glucose levels and severity of diabetic retinopathy.
14. There was no significant association found between serum creatinine levels and diabetic retinopathy.
15. There was significant negative association with haemoglobin levels and severity of diabetic retinopathy.

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CASE SHEET PROFORMA

CASE SHEET PROFORMA

Name:

Age:

Sex:

Address:

IP No. :

Presenting complaints:

H/o Presenting illness:

Past History:

1)Diabetes Mellitus

2)Hypertension

3)Any other systemic illness

Treatment History:

Any Oral Hypoglycemic agents or Insulin-

Any lipid lowering drungs-

Any other drugs-

History of laser treatment in eyes-

History of any intraocular injections-

History of ocular surgeries-

Family History:

Personal History:

Smoking-

Alcohol-

Physical activity-

Diet-

Systemic Examination:

Blood pressure-

Ocular Examination:

Visual acuity-

*Uncorrected-

*With Pinhole-

*Best corrected-

*Near Vision-

Eyelids and adnexa-

Conjunctiva-

Cornea-

Anterior Chamber-

Iris-

Pupil-

Lens-

Extraocular movements-

Posterior segment examination-

*Ophthalmoscopy-

*Fundus Fluorescein Angiography-

Tension-

Gonioscopy-

Other Investigations:

a) FBS

b) Serum lipid profile

c) HbA1C

d) Hb

e) Serum creatinine

MASTER CHART

SR. NO	NAME	AGE	SEX	HOSP. NO.	DIAB. RET. STATUS	FBS	T.CHOL	TG	HDL	LDL	Hb	HBA1C	CREAT
1	CHANDRIKA	56	F	O09094296	RE-PDR LE-Mod NPDR	287	159	158	23	106	12.5	12.7	0.73
2	PALANISAMY N.K.	72	M	O11072956	BE- No DR	90	150	137	48	73	12.9	6.3	2.16
3	NAGARAJ	51	M	O11079451	BE- No DR	190	161	158	38	89	14.6	6.7	0.72
4	RAJADURAI	47	M	OO422922	BE- No DR	262	216	247	38	140	14.4	10.24	0.73
5	KANNAN S.P.	54	M	O11079330	BE- No DR	141	154	147	34	96	13.9	10.97	0.83
6	RAMESH KUMAR	44	M	O11082216	BE- No DR	195	175	35	113	93	13.2	9.2	0.85
7	MUNIYANDI P.	55	M	O08031315	BE- PDR	210	150	140	39	141	13.2	11.9	0.9
8	SADAYAPPAN P.	61	M	O11083058	BE- No DR	162	197	229	39	134	15.4	8.23	1.22
9	DAICY	47	F	O06025684	RE- No DR LE- PDR	301	194	190	32	131	12.8	12.7	0.49
10	JAGADESAN K.S.	62	M	O11091550	BE- Mod NPDR with Maculopathy	261	170	141	33	135	13.9	10.2	1.0
11	GOWRI KALA	40	F	O11090881	RE- No DR LE- Mild NPDR	235	150	105	30	100	11.9	10.4	0.48
12	FATHIMA BEEBI	53	F	O02209828	BE- Mild NPDR	259	120	116	40	90	12.3	11.0	1.01
13	LAKSHMI R.	61	F	O03016408	BE-Mod NPDR with Maculopathy	95	106	82	38	42	12.5	7.2	1.02
14	POUJINISHA	42	F	O12005885	RE-No DR LE-Mild NPDR	137	166	140	38	91	12.1	7.0	0.86
15	SRIRAMALU	77	M	O12004036	RE-No NPDR LE-Mild NPDR	138	157	282	29	91	11.8	7.0	1.37

SR. NO	NAME	AGE	SEX	HOSP. NO.	DIAB. RET. STATUS	FBS	T.CHOL	TG	HDL	LDL	Hb	HBA1C	CREAT
16	SHANMUGA DURAI	68	M	O11093013	BE- No DR	105	160	171	35	87	12.4	6.8	0.79
17	BALA SUNDARAM	67	M	O04045592	BE- No DR	132	127	184	23	76	14.1	7.8	0.88
18	LAKSHMI N.	65	F	O02024399	BE- Mod NPDR with Maculopathy	113	170	67	61	96	13.1	7.0	0.68
19	BALAKRISHNAN	63	M	O08094907	BE- No DR	85	157	114	39	96	12.5	5.96	1.1
20	GUNASEKHARAN T.	60	M	O05011197	BE- No DR	107	128	71	37	74	10.8	5.5	0.79
21	PREMA DORTHY	50	F	O12023197	BE- No DR	132	220	142	60	146	12.9	9.0	0.62
22	VELUSAMY P.	52	M	O00019018	BE- Mod NPDR	131	274	201	33	192	13.9	8.1	0.68
23	CHELLAMMAL P.	66	F	O12027554	RE-Maculopathy, LE- Mod NPDR	363	131	126	42	81	12.7	13.01	0.58
24	DHARMARAJ A.	47	M	O11091830	RE-Mild NPDR, LE- No DR	188	281	117	58	201	14.7	9.36	0.67
25	S. KAMALAM	55	F	O10002061	BE- No DR	138	194	74	49	139	14.8	6.4	0.54
26	RAJESHWARI	55	F	O12030419	RE-Severe NPDR, LE- PDR	144	158	93	28	116	10.7	8.22	1.1
27	IRUDAYA MARY	75	F	O11042516	BE- PDR	73	115	287	5	23	8.4	7.9	1.0
28	KULANDAIRAJ	63	M	O12076177	BE-Mod NPDR with Maculopathy	183	219	158	37	150	12.3	8.7	1.1
29	NOORJAHAN	55	F	O13041234	BE-No DR	198	315	218	46	235	12.9	9.6	0.51
30	NAVANEETHA KRISHNAN	50	M	O13041232	BE- PDR	233	270	672	37	157	16.1	10.2	0.72

SR. NO	NAME	AGE	SEX	HOSP. NO.	DIAB. RET. STATUS	FBS	T.CHOL	TG	HDL	LDL	Hb	HBA1C	CREAT
31	MYILSAMY M.	50	M	O13041464	RE- Mild NPDR LE- No DR	146	224	411	42	49	16.5	9.5	0.76
32	ARUKKANI D.	45	M	O13041524	BE-No DR	190	178	102	32	126	10.9	7.8	0.7
33	THAMBURAJ	50	M	O13041707	BE-Mild NPDR	226	99	64	42	49	15.7	10.5	0.71
34	JAYAMANI	57	F	O13036972	BE- Severe NPDR	92	132	160	35	65	11.1	14.1	0.66
35	RAMASAMY K	53	M	O13042737	BE- No DR	72	172	134	33	114	12.1	6.2	0.60
36	MARUTHAM P	46	M	O13042725	BE- No DR	226	196	174	27	138	15.1	7.4	0.76
37	JALAJI RANI	63	F	O13043582	RE-Mild NPDR LE-No DR	205	210	144	68	124	12.2	9.8	0.53
38	YOGARAJAN	47	M	O13020917	BE-No DR	310	175	95	35	119	16.2	11.4	0.94
39	SELVARAJ ME	47	M	O13044672	BE-No DR	145	122	110	29	74	12.0	7.0	0.64
40	PAPATHY P	70	F	O13044719	BE-No DR	155	269	171	60	184	13.1	8.3	0.51
41	SHANMUGASUNDAR	58	M	O09053976	BE-Mild NPDR	131	117	144	30	69	15.1	6.9	0.67
42	SURULIVEL R	63	M	O13043895	BE-Mild NPDR	218	128	229	9	76	14.3	7.3	1.00
43	NURULYAHASAN	63	F	O13044389	BE-No DR	151	158	218	3	3	10.4	6.72	1.00
44	STANIESLAUS	44	M	O07014978	BE-MILD NPDR	92	194	145	38	129	14.5	6.8	0.9
45	IRUDIYA SAMY	63	M	O13041484	BE-MILD NPDR	110	158	137	31	107	13.2	7.1	1.1

SR. NO	NAME	AGE	SEX	HOSP. NO.	DIAB. RET. STATUS	FBS	T.CHOL	TG	HDL	LDL	Hb	HBA1C	CREAT
46	SAKTHIVEL RP	43	M	O11047558	BE-NO DR	123	115	93	33	67	14	6.6	1.06
47	MARIMUTHU	45	M	O13049181	BE-SEVERE NPDR	91	182	140	37	125	14.4	8.9	1.1
48	GANDHIMATHI	53	F	O13049769	BE-MILD NPDR	240	202	152	36	116	12.6	9.2	0.9
49	SHANMUGHAM MK	48	M	O12013812	BE-NO DR	123	182	101	39	128	16.6	7.7	1.0
50	NATCHIMUTHU	49	M	O11015543	BE-MOD NPDR	188	310	210	40	225	10.8	9.9	0.73
51	BHAGAVATHI GOUNDER	62	M	O12064736	BE-MILD NPDR	155	146	135	36	78	13.9	6.5	0.78
52	SUBRAMANIAM PK	68	M	O13045589	BE- NO DR	110	176	91	34	133	15.9	6.3	0.76
53	PADMINI P	55	F	O13045581	BE-NO DR	211	228	215	47	161	12.6	7.5	0.47
54	THANGARAJ	65	M	O12023260	BE-MILD NPDR	96	180	75	47	140	10.9	12.57	1.07
55	ARUMUGAM	60	M	O13013656	BE-NO DR	200	168	96	25	117	13.4	13.7	0.85
56	SAROJA	61	F	O13045877	BE-NO DR	167	193	146	44	137	11.1	8.5	0.55
57	AMIRTHAM	50	F	O08026524	BE-No DR	368	142	153	39	86	12.0	12.4	0.68
58	SAJANI N	44	F	O13042804	RE-MILD NPDR LE-NO DR	294	247	97	44	194	12.0	11.9	0.67
59	RADHAKRISHNAN	61	M	I11026435	BE-PDR with MACULOPATHY	237	127	71	31	78	10.9	7.16	0.96
60	KANDASWAMY	65	M	O11083813	BE-SEVERE NPDR with MACULOPATHY	278	170	91	29	114	12.4	9.7	0.68

SR. NO	NAME	AGE	SEX	HOSP. NO.	DIAB. RET. STATUS	FBS	T.CHOL	TG	HDL	LDL	Hb	HBA1C	CREAT
61	PERUMAL A	57	M	O10101592	BE-PDR	122	134	70	45	72	10.4	10.6	1.10
62	PARAMASIVAM	60	M	O06057850	BE-MILD NPDR	99	220	153	38	149	11.8	7.4	1.0
63	BALASUBRAMANIAM	61	M	O07023989	BE-MILD NPDR	121	146	89	29	98	13.8	6.2	0.83
64	SAKTHIVEL K	46	M	O12012837	BE-SEVERE NPDR	230	225	400	43	118	15.0	8.5	0.8
65	LALITHA	56	F	O12032046	BE-MOD NPDR	118	216	455	31	110	12.2	7.8	0.69
66	THANGAVEL	64	M	O13040862	BE-MILD NPDR	137	188	161	44	119	14.4	8.7	0.79
67	SHANMUGASUNDARAM	58	M	O09053976	BE-MILD NPDR	131	117	144	30	69	15.1	7.6	0.67
68	SANTHA BALAKRISHNAN	76	F	O13046848	BE-MILD NPDR	130	228	200	38	128	11.8	7.5	0.89
69	GEETHA A	49	F	O13046653	BE-NO DR	75	198	78	43	124	12.8	9.4	0.78
70	PADMAVATHY	72	F	O96006352	BE-MILD NPDR	128	220	84	39	136	12.6	7.9	0.9
71	SANTHA BALAKRISHNAN	76	F	O13046848	BE-MILD NPDR	130	228	200	38	128	11.8	6.8	0.89
72	DHANALAKSHMI	67	F	O12087322	BE-MOD NPDR	133	240	212	37	130	12.0	7.3	0.59
73	MANIKANDAN	45	M	O13046810	BE-NO DR	135	143	109	31	93	13.0	6.6	0.87
74	AISAMMA	60	F	O10076711	BE-NO DR	130	188	121	37	109	12.1	8.1	0.75
75	VISWANATHAN	58	M	O13046829	BE-MILD NPDR	84	194	130	35	64	12.6	6.1	0.68

SR. NO	NAME	AGE	SEX	HOSP. NO.	DIAB. RET. STATUS	FBS	T.CHOL	TG	HDL	LDL	Hb	HBA1C	CREAT
76	RAVIKUMAR K	57	M	O13046813	BE-NO DR	156	198	378	29	109	14.5	9.3	0.78
77	ANWAR BASHA	66	M	O13047405	MILD NPDR	112	202	193	30	151	15.6	8.7	0.76
78	ANAND KUMAR J	43	M	O13046184	MOD NPDR WITH MACULOPATHY	88	198	173	23	147	14	6.6	0.65
79	RAHMATHULLA	40	M	O13047970	NO DR	189	185	182	34	128	14	9.7	0.53
80	MAHESWARI	58	F	O13046257	NO DR	187	267	214	45	201	12.6	10.2	0.53
81	ABDUL JABBAR	74	M	O10010064	NO DR	168	148	168	41	88	12.9	12.4	0.70
82	ABBAS	42	M	O12051027	NO DR	99	124	69	59	57	14.3	6.1	0.8
83	POONGODI	40	F	O09057256	NO DR	141	160	123	33	102	11.1	7.4	0.8
84	MR RAMAKRISHNAN	63	M	O05039626	NO DR	121	164	109	32	112	13.4	7.0	1.1
85	CHINNASAMY	59	M	O13046451	NO DR	109	147	70	33	105	14.0	5.6	0.82
86	PONNUSAMY GOUNDER	54	M	O00004980	MOD NPDR	461	322	183	35	259	14.2	13.07	0.9
87	PARIMALAM	57	M	O13048721	NO DR	122	139	93	39	92	13.5	7.5	0.41
88	KALAIARASAN	51	M	O13048733	MILD NPDR	112	208	93	42	158	15.4	7.1	0.58
89	THARABANU	46	F	O12007204	NO DR	96	130	65	55	53	12.8	6.5	0.71
90	KUMARASAMY	49	M	O09107105	NO DR	103	164	107	36	124	10.9	6.6	0.72

SR. NO	NAME	AGE	SEX	HOSP. NO.	DIAB. RET. STATUS	FBS	T.CHOL	TG	HDL	LDL	Hb	HBA1C	CREAT
91	GRACY MOSES	68	F	O12000399	MILD NPDR	148	122	132	37	69	11.2	7.9	0.81
92	SATHIYANARAYANA	45	M	O13020603	NO DR	182	184	115	45	100	11.5	8.7	0.74
93	PALANIAPPAN	48	M	O13048982	NO DR	234	246	341	39	167	17.2	10.2	0.77
94	MEYYAPPAN	54	M	O13035545	NO DR	98	176	119	39	130	13.9	6.5	0.65
95	PALANIAMMAL	52	F	O13035575	MILD NPDR	92	170	134	40	116	13.3	6.4	0.50
96	VELUSAMY	42	M	O13013500	NO DR	107	186	102	39	132	15.3	7.7	0.65
97	LAKSHMI	55	F	I13020725	MOD NPDR	191	173	291	6	29	10.2	10.78	0.9
98	DEVARAJ	61	M	O11060264	MILD NPDR	245	205	137	37	148	16.5	9.84	0.75
99	RAMASAMY	45	M	O13049513	SEVERE NPDR	248	131	71	38	83	11.7	10.30	0.85
100	BASKARAN A	44	M	O12022613	PDR	113	127	74	45	70	11.9	8.7	0.80

ABBREVIATIONS

DM: DIABETES MELLITUS

IDDM : INSULIN DEPENDENT DIABETES MELLITUS

NIDDM : NON-INSULIN DEPENDENT DIABETES MELLITUS

DR: DIABETIC RETINOPATHY

NPDR: NON PROLIFERATIVE DIABETIC RETINOPATHY

PDR: PROLIFERATIVE DIABETIC RETINOPATHY

DME: DIABETIC MACULAR EDEMA

CSME: CLINICALLY SIGNIFICANT MACULAR EDEMA

IRMA : INTRA RETINAL MICROVASCULAR ABNORMALITIES

NVD : NEOVASCULARISATION OF DISC

NVE : NEOVASCULARISATION ELSEWHERE

FBS: FASTING BLOOD SUGAR

PPBS: POST PRANDIAL BLOOD SUGAR

HBA1C: GLYCOSYLATED HAEMOGLOBIN

TGL: TOTAL TRIGLYCERIDES

TC : TOTAL CHOLESTEROL

HDL : HIGH DENSITY LIPOPROTEIN

LDL : LOW DENSITY LIPOPROTEIN

HB: HEMOGLOBIN

ETDRS : EARLY TREATMENT DIABETIC RETINOPATHY STUDY

BMES : BLUE MOUNTAIN EYE STUDY

CURES : CHENNAI URBAN RURAL EPIDEMIOLOGICAL STUDY

WESDR : WISCONSIN EPIDEMIOLOGY STUDY OF DIABETIC RETINOPATHY

DCCT / EDIC : THE DIABETES CONTROL AND COMPLICATIONS TRIAL/EPIDEMIOLOGY OF DIABETES INTERVENTIONS AND COMPLICATIONS RESEARCH GROUP

UKPDS : UNITED KINGDOM PROSPECTIVE DIABETES STUDY